CB 12/82/01

PB82-931301

NCI/ICRDB/CB12 82/01

ICRDB CANCERGRAM

CELL BIOLOGY

Cytogenetics

SERIES CB12 No. 82/01

JANUARY, 1982

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CLINICAL STUDIES OF CHROMOSOMES IN HUMAN CANCER

1. KARYOTYPIC PATTERNS AND THEIR CLINICAL SIGNIFICANCE IN POLYCYTHEMIA VERA.

Testa JR, Kanofsky JR, Rowley JD, Baron JM, Vardiman JW
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Am J Hematol; 11(1):29-45 1981

We studied a series of 34 polycythemia vera (PV) patients to determine the incidence of chromosome abnormalities and their relationship to leukemic transformation. Metaphase chromosomes from bone marrow or unstimulated peripheral blood were examined with conventional stain and, in 20 patients, also with banding techniques. The overall incidence of clonal abnormalities in first samples were 44% (15 of 34 patients), with a higher incidence in patients who had received prior therapy. The most frequent abnormalities were long-arm deletion of No. 5 (5q-; 4 patients), gain of all or most of a No. 8 (5 patients), gain of all or most of a No. 9 (4 patients), and long-arm deletion of No. 20 (3 patients); these sometimes occurred in combination. Some of the PV patients who had cytogenetic abnor-

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malities early in the disease have had long survivals without developing leukemia. For example, one patient has been 48,XX,+8,+9 in sequential samples obtained over the last 15 yr. Five patients developed acute myeloblastic leukemia (AML); each had a complex chromosomal pattern. Two of these patients were cytogenetically normal during the polycythemic phase; the change in karyotype occurred with the leukemic transformation. Three AML patients were studied only in the leukemic phase. Three AML patients had a 5q-, and a fourth showed loss of a B-group chromosome. Evolutionary changes in the karyotype during the disease course and the occurrence of a 5q- appear to be associated with a terminal phase of PV. (Author abstract) (33 Refs)

2. ABNORMALITIES OF CHROMOSOME NO. 1 RELATED TO BLOOD DYSCRASIAS: STUDY OF 10 CASES.

Miyamoto K, Hamasaki K, Kitajima K, Adachi T, Tanaka T, Sato J
Dept. Pathology, Cancer Inst., Okayama Univ. Medical Sch., Okayama 700, Japan
Acta Med Okayama; 35(2):137-141 1981

Cell lines and primary cells derived from patients with hematologic disorders were studied by chromosome banding techniques. Ten cases with nonrandom chromosomal abnormalities affecting chromosome 1q were found in 25 cases examined. The lymphoproliferative disorders included two cases of non-African Burkitt's lymphoma, two adult T-cell leukemias, one myelofibrosis, one chronic lymphocytic leukemia, one malignant lymphoma primarily in the brain, and three chronic myelocytic leukemias in blastic crisis. The partial karyotype of the 10 cases showed an excess of the long arm of chromosome 1: 2 had reduplication of partial regions of the long arm, 2 had an additional chromosome 1q, and the remaining 6 had translocation affecting the chromosome. The bands 1q25-q32 were found to be common excess regions in all the cases. Two cases showed partial tetrasomy of the specific region (q25-q32), seven showed partial trisomy, and one showed a mosaic of partial trisomy and tetrasomy. The break points on chromosome 1 were at centromere, q12, q21, q23, q25, and q32. The study indicated that involvement of the region (q25-q32) of chromosome 1 in translocation or duplication occurs not only in myeloid cells but also in lymphoid cells. (15 Refs)

3. DOUBLE MINUTE CHROMOSOMES IN A CASE OF ACUTE MYELOGENOUS LEUKEMIA RESISTANT TO CHEMOTHERAPY.

Cooperman BS, Klinger HP
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Cytogenet Cell Genet; 30(1):25-30 1981

Double minute (dmin) chromosomes were found in 17% of bone marrow cells in a 66-yr-old woman with acute myelogenous leukemia (AML) which was resistant to treatment with cytosine arabinoside and daunorubicin hydrochloride. She died within 3 wk of developing symptoms. The cells had a range of 36 to 49 chromosomes with a mode of 47 and a variety of structural and numerical chromosome abnormalities, as well as the presence of 1 to 10 C-chromatin negative dmins. In leukemias few cases with dmins have been reported. However, we suspect other cases may have been overlooked because of the very small size of some dmins. We hope that this report will direct attention to the presence of dmins in leukemic cells and, in particular, stimulate attempts to determine if there is a correlation between their presence and the resistance of the cells to chemotherapy or the rate of disease progression. (Author abstract) (12 Refs)

4. EXPRESSION OF SILVER-STAINED NUCLEOLAR ORGANIZING REGIONS (AG-NORS) IN HUMAN CANCER.

Trent JM, Carlin DA, Davis JR
Dept. Internal Medicine, Cancer Center, Univ. Arizona, Tucson, AZ, 85724
Cytogenet Cell Genet; 30(1):31-38 1981

Five cases of ovarian adenocarcinoma, three cases of endometrial adenocarcinoma, and one case of transitional cell carcinoma of the bladder have been studied for expression of silver-stained nucleolar organizing regions (Ag-NORs). The modal chromosome number of these tumors varied from 37 to 72, with a wide range of chromosome numbers (13 to 150). The modal number of Ag-NORs in this sample varied from three to seven. Regression analysis among and between tumors demonstrated a proportionate increase in the number of Ag-NORs with increasing number of total chromosomes and increasing number of acrocentric chromosomes ($r = 0.64$ and 0.75, respectively). Modal assessment of Ag-NORs in both peripheral blood lymphocytes (PBLs) and cultured tumor cells in one patient revealed identical modes in normal and malignant cells. Also, no difference in the expression of Ag-NORs was observed between tumor cells obtained at biopsy and placed for 48 hr in agar culture and tumor cells established in finite monolayer culture. Our study provides further evidence for a proportionate increase in Ag-NORs with increasing numbers of acrocentric chromosomes and total chromosomes. (Author abstract) (22 Refs)

5. ANALYSIS OF C BANDS IN HAEMATOLOGICAL DISORDERS.

Labal de Vinuesa M, Slavutsky I, Larripa I, De Salum SB
Instituto de Investigaciones Hematologicas 'Mariano R. Castex', Academia Nacional de Medicina, Pacheco de Melo, 3081, Capital Federal (1425), Argentina
Sangre (Barc); 26(3):319-323 1981

The variations in size and form of heterochromatin observed in normal populations are called polymorphisms. In patients with malignancies the number of such variations is increased. A study of the heteromorphism of chromosomes 1, 9, and 16 was performed in 20 normal subjects, in 32 patients with hematological malignancies and in 10 patients with preleukemia. Significant differences were found with respect to the control group in leukemia (p less than 0.001) and lymphoma (p less than 0.05) but not in preleukemia. Chromosome 1 was characteristically involved, this being the only pair with differences with regard to the control group in leukemia and lymphoma; the pericentric inversion of the chromosome was the most remarkable finding. (Author abstract) (14 Refs) (In SPA)

6. C-BANDING STUDIES IN PATIENTS WITH PH(1)+ CHRONIC GRANULOCYTIC LEUKAEMIA.

Rajasekariah P, Garson OM
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Pathology; 13(2):197-203 1981

The bone marrow chromosomes of 15 patients with Ph(1)+ chronic granulocytic leukemia were studied, using both G- and C-banding. In all cases the Ph1 chromosome was formed by the translocation between chromosomes 9 and 22 and the material from chromosome 22 was found to be translocated randomly onto one or other of the pair of 9 chromosomes. Preliminary results suggest that when the translocation was on the 9 chromosome having a smaller C-band, additional abnormalities occurred in blastic transformation, whereas when the 9 chromosome with the larger C-band was involved in the translocation, additional abnormalities were not found in blastic transformation. These observations require confirmation from a larger series. C-banding also showed that there was a greatly increased heteromorphism of the C-band areas of the chromosome pair 9 in this disease, and an increased heteromorphism in the C-bands of chromosome pair 1, when compared with a control group. (Author abstract) (20 Refs)

7. SIGNIFICANCE OF NON-STANDARD PHILADELPHIA CHROMOSOMES IN CHRONIC GRANULOCYTIC LEUKAEMIA.

Potter AM, Watmore AE, Cooke P, Lilleyman JS, Sokol RJ
Centre for Human Genetics, 117 Manchester Road, Sheffield S10 5DN, England
Br J Cancer; 44(1):51-54 1981

One hundred and nineteen unselected and similarly treated patients with Ph1-positive chronic granulocytic leukemia (CGL) had the precise nature of their chromosome rearrangements producing the Ph1 studied to determine whether this had any clinical relevance. Eighteen (15%) did not have the usual 9/22 translocation and these, by life-table analysis, had a significantly shorter benign phase of their disease than the others (p less than 0.01). It further appeared that possession of a non-standard Ph1 was related to age, in that whereas only 24 patients were over 60 at diagnosis, 9 (33%) had a non-9/22 translocation (p less than 0.01). As the duration of the benign phase seemed to be shorter in those over 60 irresp ective of Ph1 type (p less than 0.01), the question arose whether non-standard PhI chromosomes were simply occurring in older patients or whether they were affecting prognosis independently. Their independent effect was suggested by the 11 patients under 60 with a non-9/22 Ph1 who still had a significantly shorter benign phase than the 84 of similar age with a standard Ph1 (p less than 0.01). It is concluded that the myeloid karyotype can provide prognostic as well as diagnostic information in patients with CGL. (Author abstract) (7 Refs)

8. CYTOGENETIC STUDIES IN CHRONIC MYELOGENOUS LEUKEMIA.

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Abteilung fur Klinische und Arbeitsmedizin, Universitat Ulm, Postfach 4066, 7900 Ulm, W. Germany
Sangre (Barc); 26(3):291-299 1981

Cytogenetic studies were performed on 45 cases of chronic myelogenous leukemia, 32 in the chronic phase, 8 in the acute phase, and 5 in both phases. Twenty-five patients were studied by the trypsin-Giemsa band technique and 20 with the Giemsa technique. The standard translocation, t(9;22) was identified in 24 of the cases studied by the band method. One case showed a complex translocation involving chromosomes 6, 9, 11 and 22. Alterations added to the Ph1 chromosome during the chronic phase were found in 19% of the cases. In the acute phase the karyotype alterations evolved in 87% of the patients, including, besides the Ph1 chromosome, a second Ph1, 17q isochromosome, and/or trisomy for chromosome 8. (Author abstract) (28 Refs) (In SPA)

9. PRESENCE OF THE PHILADELPHIA CHROMOSOME (PH(1)) IN POKEWEED MITOGEN STIMULATED LYMPHOCYTES DURING CHRONIC PHASE OF CHRONIC MYELOCYTIC LEUKEMIA (CML).

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Cancer Genet Cytogenet; 4(1):39-44 1981

There has been a lack of direct cytogenetic studies on lymphocytes in the chronic phase of chronic myelocytic leukemia (CML). Peripheral blood mononuclear cells from seven patients in the chronic phase and one in the blastic phase of Ph1-positive CML were cultured in the presence of phytohemagglutinin (PHA) and pokeweed mitogen (PWM). Preparations adequate for analysis were obtained from eight PHA and five PWM stimulated cultures. Cytogenetic studies on the PWM stimulated cultured cells revealed, in one patient, the presence of the Philadelphia chromosome (Ph1) in 23/25 metaphases. The PHA stimulated lymphocytes from the same patient were all Ph1 negative. Lymphocytes from PHA and PWM stimulated cultures from the other six patients in the chronic phase and the one patient in blastic crisis were all Ph1 negative. The one positive result suggests that some B lymphocytes contain the Ph1 and that there is a common hematopoietic stem cell for B lymphocytes as well as the myeloid, erythroid, and megakaryocytic series. (Author abstract) (14 Refs)

10. HEMATOLOGICAL AND CLINICAL MANIFESTATIONS OF THE INITIAL STAGES OF CHRONIC MYELOCYTIC LEUKEMIA.

Tokuhiro H, Hirasawa Y, Kuto F, Nagaoka T, Hayashi M
Dept. Internal Medicine, Kitasato Univ. Sch. Medicine, Kitasato, Japan
Rinsho Ketsueki; 22(4):433-443 1981

Clinical features of the initial stage of chronic myelogenous leukemia (CML) were investigated in 48 patients (25 men, 23 women), 47 of whom had the Philadelphia chromosome. One feature especially common among men with the CML was peptic ulcer (16/48); the mean age of the men with CML and peptic ulcers that were observed prior to the diagnosis of CML was higher than that of the men who had CML but not peptic ulcers. Repeated radiologic examinations for the peptic ulcers were thought to be associated with the cause of the CML. WBC counts in 9/16 patients who were followed hematologically prior to diagnosis of CML remained at approx 10,000 count levels for 3.5-5.9 mo and then increased to 30,000 levels over a 1.5-5.7 mo period. The increases in the WBC counts were not simply linear but showed periods of decrease throughout the general increasing trend. Increased numbers of basophils were also observed from the early stages of the disease. (20 Refs) (In JPN)

11. CLINICAL-HAEMATOLOGICAL ASPECTS OF SUBACUTE MYELOMONOCYTIC LEUKEMIA: A STUDY OF SEVEN CASES.

Chelazzi G, Dozio F, Piccinelli O, Rossi D
Reparto di Medicina Generale, Ospedale 'Filippo Del Ponte', Via Filippo Del Ponte, num. 19, 21100 Varese, Italy
Sangre (Barc); 26(3):300-308 1981

The clinical and laboratory data from seven patients with subacute myelomonocytic leukemia are reported. This is a malignant dysplastic-proliferative disorder characterized by peripheral monocytosis, often atypical, plus dyshemopoietic, hypercellular bone marrow with partial leukoblastosis and ill-defined 'hiatus leukemicus'. The mean age at diagnosis in the series was 67.8 yr, ranging from 54 to 81 yr. The most common presenting feature was anemia (mean Hb, 9 g/dl), shown by all the patients, while three had thrombocytopenia as well; WBC counts ranged between 2,000 and 17,300 per cu mm. The bone 07 marrow was persistently hyperplastic, with abnormalities either in the red cells (megaloblastoid erythropoiesis) or in the myeloid cells (presence of 'paramyeloid' cells with characteristics between those of the myelocytes and the monocytes), or even in the megakaryocyte cell line (hyper- or hypo-segmented nuclei). Five patients had splenomegaly. The cytogenetic studies performed in five cases failed to disclose any specific chromosome abnormality. Serum lysozyme was increased in all the patients. All patients have died, the mean survival being 8.5 mo. The diagnosis of subacute myelomonocytic leukemia is important since aggressive chemotherapy appears to shorten the survival of these patients. (Author abstract) (33 Refs) (In SPA)

12. CHROMOSOME CHANGES IN HUMAN CHRONIC LYMPHOCYTIC LEUKEMIA.

Schroder J, Vuopio P, Autio K
Folkhalsan Inst. Genetics, P.B. 819, SF-00101 Helsinki 10, Finland
Cancer Genet Cytogenet; 4(1):11-21 1981

Karyotypes were studied in B- and T-lymphocyte cultures from 66 patients with B-cell CLL and 2 patients with T-cell CLL. Thirty-one of the B-cell cases had not been treated for their disease; 35 had received radiotherapy, corticosteroids, or cytostatic drugs. Only one of the untreated patients had a clone with an abnormal karyotype. This was present in all her mitotic cells found in cultures containing lipopolysaccharide B (LPS, a B-cell mitogen) and 10% of those in cultures with pokeweed mitogen (PWM, a T- and B-cell mitogen). The karyotype of this clone was 46,XX,t(6;7),t(7;13),t(11;14). Four of the treated patients had clones with specific chromosome changes. These were 47,XY,+12 in 10% of leukoagglutinin (LA, T-cell mitogen) and protein A (PA, T- and B-cell mitogen) cultures in one case, 47,XX,+12.del(14) in 80% of LPS cultures and in all spontaneously dividing cells in another case, 46,XY,t(6;20) in all LPS cultures in another, and 46,XX,t(1;8) in all PA cultures in another. Both structural and numerical nonclonal chromosome aberrations (9%) were found in 24% of the different cultures of cells from untreated patients, and in 15% of the cells in 20% of the different cultures in the patient who had received treatment. Both patients with T-cell CLL had received treatment for their disease, and had a normal karyotype in all cultures. (Author abstract) (25 Refs)

13. ACUTE LYMPHOCYTIC AND MYELOMONOCYTIC LEUKEMIA ASSOCIATED WITH LOW PLATELET COUNTS AND 21Q- MARKER CHROMOSOME.

Alimena G, Dallapiccola M, De Cuia MR, Mandelli F, Mitelman F
Dept. Hematology, Univ. Rome, Via Chieti 7/Via Lancisi 3, I-00161 Rome, Italy
Hum Genet; 57(3):329-331 1981

The case histories of two patients (1 man and 1 woman) with acute lymphocytic and acute myelomonocytic leukemia who had a 21q- marker chromosome are reported. Both patients were thrombocytopenic at diagnosis and during the course of the disease. The platelet count was 65 x 10(9)/liter and 85 x 10(9)/liter, respectively. The deleted segment of chromosome 21 was not translocated to any other chromosome of the complement. It was concluded that 21q- marker is not related to an increased platelet count, nor limited to primary thrombocytopenia. (11 Refs)

14. BURKITT'S TYPE ACUTE LYMPHOBLASTIC LEUKEMIA. CELLULAR PHENOTYPE AND CHROMOSOME ABNORMALITIES.

Demeocq F, Bernard A, Boumsell L, Bezou MJ, Turchini MF, Malpuech G
Laboratoire d'Hematologie, Clinique Medicale Infantile, Hotel-Dieu, BP69, 69003 Clermont-Ferrand, France
Arch Fr Pediatr; 38(5):355-357 1981

The immunologic and cytogenetic analysis of a 13-yr old male patient with Burkitt's type acute lymphoblastic lymphoma is described. The lymphoblasts were found to carry IgS mu and gamma, with no IgD, and with only weak expression of the receptors for the constant fragment of IgG. This phenotype corresponded with a highly differentiated B cell line. A translocation between chromosomes 1 and 8 was observed. The implications of these findings are discussed. (12 Refs) (In FRE)

15. CULTURE OF BONE MARROW REVEALS MORE CELLS WITH CHROMOSOMAL ABNORMALITIES THAN THE DIRECT METHOD IN PATIENTS WITH HEMATOLOGIC DISORDERS.

Knuutila S, Vuopio P, Elonen E, Siimes M, Kovanen R, Borgstrom GH, De la Chapelle A
Dept. Medical Genetics, Univ. Helsinki, Haartmaninkatu 3, 00290 Helsinki 29, Finland
Blood; 58(2):369-375 1981

The effect of short-term culture on the type and frequency of chromosomal aberrations found in bone marrow cells from patients with hematologic disease was evaluated. The classic direct method (1-2 hr incubation) was compared with methods involving culture for 1-4 days with or without methotrexate. Data on 32 samples from 21 patients in whom an abnormal clone was found indicated that on 18 occasions, culture yielded a higher proportion of cells belonging to the abnormal than to the normal clone. In 10 of those cases, the difference was statistically significant (p less than 0.05). The reverse situation was seen on six occasions, none of which was statistically significant. On four occasions, the culture methods disclosed a clonal abnormality that would not have been detected if the direct method alone had been used. The phenomenon occurred in chronic myeloid leukemia, myeloid and lymphoid acute leukemia, and preleukemic conditions. It affected clones with different cytogenetic abnormalities such as 5q-, t(8;21) and i(17q). In one instance, sister chromatid staining after BUdR incorporation indicated that both cytogenetically normal and abnormal (5q-) mitoses were in their second division after 2 days in culture. The implication of these studies is that to improve the chances of detecting cytogenetically abnormal cells, bone marrow cells should be cultured. Examination of as many mitoses as possible after culture for 1-4 days may reveal abnormal clones that are sparsely represented. Finally, results obtained with different methods are not directly comparable. (Author abstract) (11 Refs)

16. DISPERMIC ORIGIN OF XY HYDATIDIFORM MOLES.

Ohama K, Kajii T, Okamoto E, Fukuda Y, Imaizumi K, Tsukahara M, Kobayashi K, Hagiwara K
Dept. Obstetrics and Gynecology, Hiroshima Univ. Sch. Medicine, Hiroshima, Japan 734
Nature; 292(5823):551-552 1981

Four XY hydatidiform moles (moles A, B, C, and D) were studied in an attempt to provide evidence that they result from the fertilization of an empty egg by two haploid spermatozoa. The macroscopic and microscopic findings of the four XY moles were indistinguishable from those of XX moles. The karyotypes of the cells cultured from the molar tissue of the four patients were 46,XY. Mole A inherited both chromosomes 15 and the histocompatibility leukocyte antigen (HLA)-B specificities exclusively from the father. Similarly, mole B showed an exclusively paternal inheritance of both chromosomes 15 and 21, as well as HLA-A and -B specificities. Mole C inherited both chromosomes 15 from the father. Mole D inherited pairs 3, 13, and 22 exclusively from the father. Thus all four moles were androgenetic. Further, each of the four moles had both homozygous (a paternal marker transmitted to the mole in duplicate) and heterozygous (both paternal markers transmitted to the mole) genetic markers. The implications of these findings for chemotherapy and prognosis are discussed. (11 Refs)

DNA CONTENT AND PLOIDY CHANGES ASSOCIATED WITH CANCER

17. ANALYSIS OF LIVER CELL DYSPLASIA AND HEPATOMAS BY FEULGEN-DNA CYTOFLUOROMETRY.

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Kyoto Furitsu Ika Daigaku Zasshi; 90(1):13-31 1981

To perform correlated cytofluorometric and histopathologic studies of liver cell dysplasia (LCD), cirrhotic liver tissues and hepatocellular carcinomas, a method for applying Feulgen-DNA cytofluorometry to paraffin-embedded tissues from autopsies has been developed. Autopsy liver specimens were fixed in neutralized formalin, and single cells were isolated with a Dounce homogenizer. The cells were treated with sodium dodecyl sulfate (0.5%, in double distilled water for 18-24 hr at 60 C and also with Carnoy's soln (methanol 3: acetate 1) for 15 min at 0-4C, to eliminate nonspecific cytoplasmic fluorescence. Smear preparations of the cells were Feulgen stained with pararosaniline hydrochloride. The nuclear DNA content of each liver cell was measured by an epiillumination cytofluorometer NIKON SPM-RF1. Cells from LCD, cirrhotic liver tissues and hepatomas of 15 autopsy cases of liver cirrhosis (including 10 cases of hepatoma) were analyzed by this method. Polyploid cells such as mononuclear tetraploid, mononuclear octaploid, and binuclear cells were increased in the cases of liver cirrhosis without either LCD nor hepatomas, compared with those of normal controls. The hepatocytes of the LCD area showed more marked polyploidization than those of the non-LCD area and cells intermediate between ploidy classes were not observed. On the other hand, the hepatoma areas consisted of many cells with intermediate values, so that the ploidy pattern of the hepatomas showed a unimodal and wide distribution with the peak value between diploid and tetraploid. The results indicate that (1) the polyploidization of the liver cells proceeds during the progression of the illness from chronic hepatitis to liver cirrhosis, (2) the LCD area consists of cells with dramatically advanced polyploidization, and (3) the ploidy pattern of hepatoma, which can be clearly distinguished by DNA-cytofluorometry from that of the LCD area, shows an increased number of cells in the DNA synthetic phase, and also shows the presence of aneuploid cells. (37 Refs) (In JPN)

18. FLOW CYTOMETRY OF BREAST CARCINOMA: 1. RELATION OF DNA PLOIDY LEVEL TO HISTOLOGY AND ESTROGEN RECEPTOR.

Olszewski W, Darzynkiewicz Z, Rosen PP, Schwartz MK, Melamed MR

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Cancer; 48(4):980-984 1981

Flow cytometry studies of the DNA distribution of tumor cells from 92 human breast cancers showed measurable aneuploidy (hyperploidy) in 85 cases (92%). The DNA ploidy values were unimodal in each case, but there was a bimodal distribution for the entire series. One group of tumors had a diploid or near diploid DNA distribution and a second group had ploidy levels from triploid to tetraploid or higher. The tumors with lower DNA ploidy (at or near diploid) tended to be histologically low grade, cytologically more orderly and estrogen-binding positive; those with higher DNA ploidy were more likely to be higher grade, more anaplastic, and estrogen-binding negative. (Author abstract) (27 Refs)

19. ELECTRON MICROSCOPIC AND MICROSPECTROPHOTOMETRIC OBSERVATIONS IN SCIRRHOUS CARCINOMA OF THE STOMACH.

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Jpn J Clin Oncol; 11(1):39-49 1981

An attempt was made to clarify the developmental behavior of scirrhous carcinoma (SC) through the use of electron microscopic and microspectrophotometric technics for estimating the DNA content of cancer cells in nine patients with SCs and five patients with well-differentiated adenocarcinomas (ACs). Electron microscopic observation of SCs revealed marked proliferation of collagen fibrils. Damaged cancer cells scattered along the collagen fibrils were prominent findings in the deep area of the lesion, but were rarely seen in the superficial and peripheral areas. In ACs, proliferation of collagen fibrils occurred to some extent, but not to the extent seen in SCs. The DNA distribution patterns in SCs, varied according to the area of the carcinoma. In the superficial and peripheral areas, the DNA content of the nuclei of cancer cell had a much wider range than that of normal tissues. Two peaks were found at the hyperdiploid and hypertetraploid ranges. The percentage of nuclei below the hyperdiploid range was higher in the deep area than in the other two areas in all nine cases. In the ACs, the histogram showed varying distributions of one to two peaks. Differences in the DNA distribution pattern according to area were not discernible. The percentages of nuclei below the hyperdiploid range were found to be almost identical among the three areas. The results suggested that the scirrhous area of the carcinoma has little significance for tumor growth and that growth can be determined from the scattered cancer cells in the edematous stroma at the periphery of the lesion. (11 Refs)

CHROMOSOMAL FRAGILITY AND GENETIC FACTORS PREDISPOSING TO HUMAN CANCER

20. LYMPHOCYTE CHROMOSOME SURVEY IN 42 PATIENTS WITH RETINOBLASTOMA: EFFORT TO DETECT 13Q14 DELETION MOSAICISM (MEETING ABSTRACT).

Motegi T, Minoda K
Department of Pediatrics and Ophthalmology, University Branch Hospital, Tokyo, Japan
International Symposium on Intraocular Tumors, May 17-20, 1981, Schwerin, W Germany European Ophthalmology Society; :A50 1981

The results of lymphocyte chromosome survey in retinoblastoma (Rb) patients using a method to detect a relatively low-proportion mosaicism of 13q14 deletion are presented. Forty-two patients with Rb (10 unilateral and 32 bilateral; 38 sporadic and 4 familial) were selected for this study. The diagnosis of Rb was confirmed by pathologic examinations of the enucleated eye in all but two familial ones. Three out of 42 patients showed abnormal karyotypes; 46, XY, del (13) (q14.1q14.3)/46, XY(the proportion of abnormal cells, 51 percent), 46, XX, del (13) (q14.1q14.3)/46, XX (The proportion of abnormal cells, 9% and 46, XY, del (13) (q14.1q21.2). No aneuploidy nor structural aberration other than (number 13 was noted. Two patients with 13q14 deletion mosaicism in this study showed normal psychomotor and somatic development at about one yr old. The patients with del (13) (q14.1q21.1) showed moderate psychomotor retardation and mild somatic retardation, but no serious anomaly except for Rb. All these 3 patients had sporadic bilateral Rb. The present mosaic cases were in the intermediate genetical position between a germ cell mutation and a somatic cell mutation, for abnormal cells might be spread throughout the body including germ cells. Three chromosome surveys of peripheral lymphocytes in the population with Rb in the literature revealed the interstitial deletion of 13q in one out of fifty, one out of thirty-three, but none out of seventeen. The relative high rate of 13q- in this study seems to be not only due to predominant number of bilateral Rb but also to the effort to detect the mosaicism. (no Refs)

21. FAMILIAL ACUTE MYELOGENOUS LEUKEMIA ASSOCIATED WITH RNA VIRUS AND POLYMORPHISM OF 1QH+.

Sadamori N, Nonaka H, Ichimaru M, Igarashi H, Hirota M, Sawada H
Dept. Genetics and Endocrinology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Cancer Genet Cytogenet; 4(1):23-30 1981

In order to investigate the genetic background of leukemogenesis of two brothers with acute myelogenous leukemia (AML), they and their family members were studied genetically, immunologically, virologically, and cytogenetically. Their parents were first cousins once removed and had the same or a very close type of human WBC antigen (HLA) and blood groups. In all five non-leukemic family members the IgG level was elevated, and in two healthy siblings the IgM level was beyond the normal range. The RNA reverse transcriptase activity in serum of the younger brother (Case 2) with AML was elevated. A cytogenetic study of the family revealed polymorphism of 1qh+. Based on these findings, we discuss the genetic and environmental factors of familial leukemia. (Author abstract) (24 Refs)

CHROMOSOMES OF HUMAN CELL LINES AND TUMORS IN VITRO

22. A HUMAN GALLBLADDER ADENOCARCINOMA CELL LINE.

Morgan RT, Woods LK, Moore GE, McGavran L, Quinn LA, Semple TU
Dept. Surgery, Div. Surgical Oncology, Denver General Hosp., W. 8th Ave. and Cherokee St., Denver, CO, 80204
In Vitro; 17(6):503-510 1981

A continuous cell line, COLO 346, was established from a liver metastasis in a patient with adenocarcinoma of the gallbladder. COLO 346 grew as an adherent monolayer of pleomorphic epithelioid cells. COLO 346 cells produced esterone, but no estradiol, progesterone, or cortisol. No ACTH, beta-subunit of human chorionic gonadotropin, carcinoembryonic antigen, or alpha-fetoprotein production by the cells was detected. Cell doubling time was 36 hr. Seven allelic isozymes were assayed. COLO 346 had a chromosome mode of 74 at 21 mo postestablishment with six marker chromosomes present in 100% of the cells analyzed. COLO 346 has been in continuous culture for over 2 yr and is available to other investigators for their studies. (Author abstract) (28 Refs)

23. IN VITRO CLONAL ASSAY FOR HUMAN METASTATIC MELANOMA CELLS.

Meyskens FL, Soehnlen BJ, Saxe DF, Casey WJ, Salmon SE
Cancer Center Div., Univ. Arizona, Tucson, AZ, 85719
Stem Cells; 1(1):61-72 1981

An in vitro clonogenic assay was used for human metastatic melanoma cells. Tumor cells obtained from skin, lymph node, and viscera were suspended in soft agar; melanoma colony formation was observed in 22 of 33 tissue samples. Serial observation with inverted light microscopy, staining of fixed colonies for melanin, and cytological and karyotypic analysis of individual cells were used to establish melanocytic tumor origin. Two morphologically distinct colony variants of apparent neoplastic origin were identified: light large cell colonies and dark small cell colonies. This clonogenic assay may prove useful in the examination of factors which affect varying growth and differentiation patterns in metastatic melanoma cells. (31 Refs)

24. CHARACTERISATION OF HODGKIN CELLS (MEETING ABSTRACT).

Diehl V, Kirchner HH, Stein H, Fonatsch C, Schaadt M
Inst. f. Pathologie, Universitat Kiel, Hannover, W. Germany
Immunobiol; 159(1/2):186 1981

To overcome the difficulties to analyze freshly isolated Hodgkin-(H) and Sternberg-Reed (SR) cells we established four in vitro cell lines from three patients with histologically proven Hodgkin's disease (L 428, L 439 from pleural effusions of different patients, L 538, L 540 from bone marrow and peripheral blood of the same patients). The neoplastic nature of the culture cells is indicated by the demonstration of several structural and numerical chromosome abnormalities associated with a monoclonal pattern of marker chromosomes. Heterotransplantion in nude mice resulted in tumor growth with all cell lines after intracranial inoculation, with the L 428 after sc transplantation embedded in a plasma clot and only with the L 540 after im inoculation. Ia-like antigens, acid phosphatase and acid esterase were found to be present in the culture cells. The L 428 and L 439 showed also receptors for human T-cells. All cell lines lacked EBV-specific antigens, surface or cytoplasmic

Ig, HTLA, receptors for C3b, C3d, IgG-Fc, mouse E or sheep E and were devoid of lysozyme, peroxidase and chloracetate esterase. These features do not correspond to that of B-cells, T-cells, myeloid cells, monocytes or macrophages. The morphology and the marker pattern of the culture cells, however, is identical with that of freshly obtained H- and SR cells, except for the lack of CIg in the in vitro cells. Antisera were raised in rabbits against the L 428 cells. After absorption with various lymphoid and myeloid cells the antiserum reacted only with L428 cells and the H and SR-cells in biopsies from 11 cases of Hodgkin's disease. These findings suggest that the L 428, L 439 and L 538/540 cell lines are indeed derived from H- and SR-cells and are helpful to define the origin and specific membrane structures of the malignant cells in Hodgkin's disease. (no Refs)

CHROMOSOMES OF ANIMAL CELL LINES AND TUMORS

25. METT-1: A KARYOTYPICALLY NORMAL IN VITRO LINE OF DEVELOPMENTALLY TOTIPOTENT MOUSE TERATOCARCINOMA CELLS.

Mintz B, Cronmiller C
Inst. for Cancer Res., Fox Chase Cancer Center, Philadelphia, PA, 19111
Somatic Cell Genet; 7(4):489-505 1981

The establishment and characteristics of a new karyotypically normal culture line of mouse teratocarcinoma stem cells is described. The primary tumor which was the source of the cell line was induced by ectopic transplantation of a day 6 postimplantation mouse embryo from the 129/Sv Sl C P inbred strain. After approx 8 wk the tumor, which now formed a visible lump was removed. The culture medium and the establishment of the cell line is described. One of the cells lines established, a euploid cell line, was designated as METT-1 (Mouse Euploid Totipotent Teratocarcinoma cell line). This cell line grew as a m onolayer with cells of uniform appearance and were characterized by a high nucleocytoplasmic ratio and fine granular cytoplasm, as seen in phase microscopy. Chromosome counts in metaphase revealed a high incidence of euploidy (92%). The high modal frequency of euploidy and very narrow range of variation continued to characterize the cell line at progressive passages in culture. Freezing and storage of the cell line in liquid nitrogen, followed by thawing and re-culturing, also caused no serious loss of euploidy as of 17 post-freezing passages. The karyotypes confirmed that the cell line had two normal X chromosomes and no Y chromosome, apparently due to origin of the experimental tumor from a chromosomally female embryo. (43 Refs)

26. ESTABLISHMENT OF CULTURED DD/TBR MOUSE MAMMARY TUMOR CELL LINES.

Iwai Y
Central Res. Inst., Radiation Center of Osaka Prefecture, Osaka, Japan
Nara Igaku Zasshi; 32(2):168-180 1981

Three mouse mammary gland cultured cell lines were established from a mammary carcinoma that spontaneously occurred in a 10-mo-old female DD/Tbr strain mouse. Two of the cell lines were epithelial (DD-762 and DD-763) type cells and one was spindle-shaped (DD-761). Except for the DD-764 cell line, the chromosome number was 80 and the population doubling time was 18 hr. These cell lines were thought to produce B-type RNA virus (MuMTV) and not murine leukemia virus (MuLV). Study of viral kinetics by means of RNA-directed DNA polymerase (RDDP) activity assay indicated that MuMTV production was observable during the stationary phase but not the logarithmic phase of cell growth. The production of the mammary tumor virus was found to be inversely dependent upon the presence of dexamethasone (DXM); MuMTV was produced in large amounts (0.8 mg viral protein/liter/day in DD-764), and the production was enhanced with the addition of DXM. (27 Refs) (In JPN)

27. CHROMOSOME INVESTIGATIONS OF THE USUBUCHI SARCOMA. I. STUDIES IN SEVEN TRANSFERS FROM THE 1812TH TO 1895TH GENERATIONS.

Obara Y, Satoh H, Saitoh K
Chromosome Res. Unit, Faculty Science, Hokkaido Univ., Sapporo, 060, Japan
Cytologia (Tokyo); 46(1):413-426 1981

Karyotypes were obtained from ascites tumor cells of the Usubuchi sarcoma (US), and maintained by successive transfers. Samples were made in the 1812th, 1815th, 1820th, 1876th, 1885th, 1887th, and 1895th transfer generations. Control karyotypes were obtained from bone marrow cells from intact normal rats. Chromosomes were stained for C- and G-bands. The diploid number for the controls was found to be 42. The chromosome numbers for the first three transfers ranged from 24 to 140. The chromosome numbers for the last four transfers ranged from 30 to 215. Both groups showed a modal number of 65, indicating a hypertriploid state with a stable modal number regardless of the number of transfer generations. The US cells contained few normal chromosomes, disomic, or trisomic homoloques. They showed several marker chromosomes, designated M1-7, not found in normal cells. Morphologically the markers resembled normal chromosomes, but banding analysis revealed differences. The presence of fragments of normal chromosomes within the markers could not be determined. The banding of each marker was essentially constant. The markers occurred in many different combinations, even in cells from the same generation. The findings suggest extensive chromosomal rearrangement during long-term serial transfer. (18 Refs)

28. BASAL LAMINA FORMATION BY NORMAL AND TRANSFORMED MOUSE MAMMARY EPITHELIAL CELLS DUPLICATED IN VITRO.

David G, Van der Schueren B, Bernfield M
(c/o Bernfield) Dept. Pediatrics, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
JNCI; 67(3):719-728 1981

Cells from low-passage (LP) cultures of a mouse mammary epithelial line (NMuMG cells) form a basal lamina when they are cultured on a Type I collagen gel substratum. A high-passage (HP) strain of this line maintained the morphologic, serologic, and karyologic properties of the LP cells. For the determination of whether transformation of the NMuMG cells might lead to defects in the basal lamina, cells from LP cultures were compared in vivo and in vitro with cells of HP cultures for tumorigenicity, growth characteristics, and ability to form a lamina. The LP NMuMG cells had a typical epithelial morphology and showed no cytologic evidence of cancer. They formed an ultrastructurally normal continuous basal lamina in vivo when they were injected into athymic nude mice. In contrast, the HP cells were pleomorphic and highly invasive when injected into nude mice where they showed frequent and large basal lamina defects. These cells also accumulated only traces of lamina-like materials when cultured on a collagen gel, indicating that neoplastic transformation had markedly reduced the ability of NMuMG cells to form a basal lamina both in vivo and in vitro. Because the collagen gel culture system duplicated the in vivo situation with regard to basal lamina integrity, the basis for this lack of in vitro basal lamina formation may be physiologically relevant for the mechanism of malignant invasion. (Author abstract) (33 Refs)

GENE MAPPING STUDIES

29. NUCLEOTIDE SEQUENCE OF THE CHROMOSOMAL GENE FOR HUMAN FIBROBLAST (BETA1) INTERFERON AND OF THE FLANKING REGIONS.

Degrave W, Derynck R, Tavernier J, Haegeman G, Fiers W
(c/o Fiers) Lab. Molecular Biology, State Univ. Ghent, Ledeganckstraat 35, B-9000 Ghent, Belgium
Gene; 14(3):137-143 1981

The nucleotide sequence of the human fibroblast (beta1) interferon chromosomal gene and its flanking regions were determined. The chromosomal EcoRI fragment of plasmid pgHFIF-4, a recombina nt derivative of pBR325, contained the genomic beta1 interferon DNA. Plasmid DNA was prepared by lysozyme-detergent lysis and purified by isodensity centrifugation in CsCl gradients in the presence of ethidium bromide. Dephosphorylation, 5'-terminal labeling, and nucleotide sequence analysis of the DNA fragments were performed using 0.5 mm, 5-10% polyacrylamide gels. A preliminary restriction map of the interferon gene-flanking regions was determined and provided a basis for the nucleotide sequence analysis. Chemical degradation showed the sequence to comprise the 836 base pair (bp) segment corresponding to mRNA data, preceded by a 290 bp sequence up to the EcoRI site of the subcloned DNA fragment, and followed by a downstream sequence of approx 190 bp. No intervening sequences were found in the gene. The upstream region contained an abundance of purines. Four homologous segments were discerned: A at position-31, the Hogness-Goldberg box, B at-93 to-85, presumed the transcription recognition region, C at-57 to-51, and D at-114 to-105. A continuous A+T-rich sequence of some 190 bp flanking the gene downstream was established, an area which showed clear but weak homology with the same region in alpha1 interferon. In the upstream sequence, however, significant homologies were found to extend from position-1 up to at least-135, including segments A, C, and D. (31 Refs)

30. MAPPING OF THE FV-4 MOUSE GENE CONTROLLING RESISTANCE TO MURINE LEUKEMIA VIRUSES.

Ikeda H, Sato H, Odaka T
Dept. Genetics, Inst. Medical Science, Univ. Tokyo, 4-6-1 Shirokanedai Minatoku, Tokyo 108, Japan
Int J Cancer; 28(2):237-240 1981

Fv-4, a gene controlling susceptibility to ecotropic murine leukemia viruses, was linked to both Pre-I (prealbumin) and Igh-I (immunoglobulin heavy-chain constant region) loci on chromosome 12 in mice. The gene order was Fv-4-Pre-I - Igh-I, and the estimated frequency of recombination between Fv-4 and Pre-I was about 20%. (Author abstract) (29 Refs)

31. LY-M19: THE LYB-2 REGION OF MOUSE CHROMOSOME 4 CONTROLS A NEW SURFACE ALLOANTIGEN.

Tada N, Kimura S, Liu Y, Taylor BA, Hammerling Y
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Immunogenetics; 13(6):539-546 1981

Spleen cells from an SJL mouse immunized with 70Z/3 cells, an established pre-B cell line, were fused with cells of the nonsecretor myeloma line NS.1. One established hybridoma cell line (clone K10.6) continuously secreted antibody that recognized a new antigenic specificity tentatively named Ly-m19. This newly found antigen is detectable on both T and B cells. Cytotoxicity assays reveal that 75% of the spleen and lymphnode cells, 35% of bone marrow cells, and 15% of thymus cells reacted with antibody of clone K10.6. Strains expressing the specificity Ly-m19.1 are characterized by negative reactions and include the strains AKR, CE/J, RF/J, GR/A, SJL, P/J, BDP/J, and LG/J. All other strains so far tested are Ly-m19.2. This strain distribution pattern distinguishes Ly-m 19 from any known murine lymphocyte alloantigen, but it parallels the Lyb-2c haplotype. Linkage test of a set of AKXL recombinant inbred strains revealed close linkage of Ly-m19 and Lyb-2 loci on mouse chromosome 4. (Author abstract) (24 Refs)

32. A NEW MOUSE CELL-SURFACE ANTIGEN (LY-M18) DEFINED BY A MONOCLONAL ANTIBODY.

Kimura S, Tada N, Liu Y, Hammerling U
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Immunogenetics; 13(6):547-554 1981

Spleen cells from C3H/An mice immunized with spleen cells of C57BL/6-H-2k mice were fused with myeloma cell line NS.1. One established hybrid cell line continuously secreted antibody that recognized a new surface antigen provisionally called Ly-m18. The new alloantigen is expressed on 90% of thymus cells, 55% of spleen cells, and 45% of either lymphnode or bone-marrow cells. It is also expressed on cells derived from brain, kidney, and liver. Fifty percent of either peripheral T or B cells express the Ly-m18 antigen, and some tumor cell lines with T, B, pre-B or stem cell characteristics are Ly-m18 (+). The strain distribution pattern distinguishes Ly-m18 antigen from all other murine lymphocyte alloantigens. The typing data of two sets of CXB and AKXL recombinant inbred strains indicate that the Ly-m18 gene is linked to the Ltw-2 locus which has not yet been assigned to a chromosome. (Author abstract) (30 Refs)

33. NEW MOUSE IMMUNOGLOBULIN A HEAVY CHAIN ALLOTYPE SPECIFICITIES DETECTED USING THE HYBRIDOMA-DERIVED IGA OF I/ST MICE.

Tada N, Kimura S, Binari R, Liu Y, Hammerling U
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Immunogenetics; 13(6):475-481 1981

Immunizations of C57BL/6 and A mice with IgA derived from the I/St mouse strain yield alloantisera which detect two allotypic determinants of IgA. The two determinants display discrete strain distributions. The first, identified by the alloantiserum C57BL/6 anti-IgA of I/St strain hybridoma ID150, follows the Ighc haplotype, and the second, identified by the alloantiserum A anti-IgA of I/St strain hybridoma ID150, correlates with Ighc and Ighb haplotypes. Absorption with monoclonal IgM, which has the same idiotype as the ID150 IgA clone, removed idiotype-specific antibodies from both alloantisera. The remaining antibodies are directed against determinants associated with the alpha chain constant region, as shown by absorption with monoclonal IgA. By use of recombinant inbred strains of mice and mice congenic at the Igh locus, the loci controlling both Calpha allotypic determinants have been mapped to the Igh region on chromosome 12. (Author abstract) (16 Refs)

MOLECULAR CYTOGENETICS

34. GENE AMPLIFICATION IN MOUSE TUMOR CELL LINES.

Martinsson T, Lundh L, Tenning P, Levan G
Dept. Genetics, Univ. Gothenburg, Gothenburg, Sweden
Cell Biol Int Rep; 5(8):772 1981

Several lines from the mouse ascites tumor SEWA were tested for methotrexate (MTX) resistance (r) and associated changes in chromosomal features. The SEWA tumor lines were highly MTX sensitive, but on prolonged exposure to increasing MTX doses, one of the lines developed MTXr at 10 ug/ml. Development of MTXr was associated with the appearance of double minute chromosomes (DM). Found even in cells resistant to 0.1 ug/ml, the DM were large and uniform in size, with av 6.6 DM/cell. Gradual increase to 10 ug/ml MTX increased the av number to 36.9 DM/cell. At the higher concentrations DM size varied, with many cells displaying much smaller DM. Homogeneously staining regions (HSR) originally present in this line persisted unchanged. The development of MTXr was accompanied by greatly increased production of a 20,000 mol wt intracellular protein whose wt correlates with that of mouse dihydrofolate reductase, the target enzyme for MTX. (4 Refs)

35. ACCESSIBILITY OF SOME REGIONS OF CHROMATIN OF LEUKEMIC CHICKEN CELLS TO SINGLE STRAND NUCLEASE S1.

Leibovitch SA, Guillier M, Harel J
Laboratoire de Biologie Moleculaire et Physiopathologie Cellulaire, Institut Gustave-Roussy, G. R. N. 8 du CNRS, 16 bis, Avenue Paul Vaillant Couturier, 94800 Villejuif, France
Biochem Biophys Res Commun; 101(3):719-726 1981

Single strand nuclease S1 was used to probe the structure of DNA in Avian leukemic cells infected with Avian Myeloblastosis virus (AMV). Acid-soluble DNA fragments released after incubation of purified nuclei with 2000 units/ml (Aspergillus oryza) nuclease S1 appeared after a 5 min lag, with quantities increasing rapidly to approx 2% of total nuclear DNA at 20-30 min and to approx 4% after 4 hr. Control samples incubated without S1 released less than 1% of total DNA after 3 hr. Size distribution of the purified DNA was determined by agarose slab gel electrophoresis. Between 0-5 min of nuclease digestion only high mol wt (greater than 12,000 base pair) DNA fragments were obtained. Thereafter low mol wt segments appeared which could be resolved into at least the four size classes monomer through tetramer. A comparison of the effects of S1 nuclease and DNAase I on integrated AMV provirus sequences was made by hybridization of enzyme-treated nuclei to AMV-3HcDNA. Partial digestion of leukemic cell DNA with S1 nuclease did not significantly modify hybridization from the greater than 80% level found with non-nuclease-treated DNA. With DNAase I, however, hybridization of the virus-specific probe was reduced nearly to the 20% level obtained with normal embryonic chick cell DNA. S1 nuclease and DNAase I appear not to recognize the same sites in active chromatin regions. Furthermore, a limited number of chick leukemic cell DNA sites were susceptible to S1 nuclease. The resulting DNA fragments appearing as multiples of a monomeric unit were similar to fragments produced by micrococcal nuclease digestion. (18 Refs)

36. MOLECULAR CLONING OF THE AVIAN MYELOCYTOMATOSIS VIRUS GENOME AND RECOVERY OF INFECTIOUS VIRUSES BY TRANSFECTION OF CHICKEN CELLS.

Vennstrom B, Moscovici C, Goodman HM, Bishop JM
Dept. Microbiology, Biomedical Center, Uppsala, Sweden
J Virol; 39(2):625-631 1981

The avian retrovirus myelocytomatosis virus 19 (MCV) possesses an interesting diversity of oncogenic potentials, but the virus has proven difficult to study because of its inability to replicate without the assistance of a helper virus. We have therefore isolated and amplified the genome of MCV by molecular cloning in a prokaryotic vector. The topography of the cloned DNA was explored by the use of restriction endonucleases and radioactive complementary DNAs representing specific domains in avian retrovirus genomes. The cloned DNA appeared to be an authentic representation of the MCV genome: the size and genetic topography of the DNA were comparable to those of MCV, and transfection of the cloned DNA into chicken cells (in company with the DNA of a suitable helper virus) gave rise to virus with the genome and transforming potentials of MCV. The availability of cloned MCV DNA should facilitate a variety of genetic and biochemical manipulations directed at elucidating the mechanism of oncogenesis by MCV. (Author abstract) (25 Refs)

37. A ROUS SARCOMA VIRUS PROVIRUS IS FLANKED BY SHORT DIRECT REPEATS OF A CELLULAR DNA SEQUENCE PRESENT IN ONLY ONE COPY PRIOR TO INTEGRATION.

Hughes SH, Mutschler A, Bishop JM, Varmus HE
Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11724
Proc Natl Acad Sci USA; 78(7,part2):4299-4303 1981

The Rous sarcoma virus (RSV)-transformed rat cell line RSV-NRK-2 contains a single complete RSV provirus. We have obtained recombinant lambda clones that contain both ends of the RSV provirus and the flanking rat sequences. The provirus is integrated in unique DNA and is present in only one of the two homologous chromosomes. The rat sequences into which the RSV provirus integrated were also cloned from the RSV-NRK-2 cell line. The sequences of the regions involved in the recombination event have been determined and compared. Our data suggest that, compared with the sequence of viral DNA in the large circular form of unintegrated viral DNA, the provirus lacks two base pairs at each end and that the provirus is flanked by a six-base-pair direct repeat of cellular DNA. This six-base-pair repeat was apparently created during the integration event because this sequence was present only once at the integration site before the provirus was inserted. A survey of eight other independent RSV transformed rat cell lines demonstrates that, in agreement with earlier results, the RSV proviruses have entered different segments of rat cell DNA. We have also determined the sequence of a second virus DNA-host cell DNA junction from a second RSV-transformed rat cell line (RSV-NRK-4) and find that there are no obvious similarities between the two integration sites or between the integration sites and the termini of viral DNA. (Author abstract) (32 Refs)

38. CELL CYCLE REGULATION OF DNA REPAIR IN NORMAL AND REPAIR DEFICIENT HUMAN CELLS.

Gupta PK, Sirover MA
Dept. Pharmacology, Temple Univ. Sch. Medicine, 3420 North Broad St., Philadelphia, PA, 19140
Chem Biol Interact; 36(1):19-31 1981

The regulation of nucleotide excision repair and base repair by normal and repair deficient human cells was determined. Synchronous cultures of WI-38 normal diploid fibroblasts and Xeroderma pigmentosum fibroblasts (complementation group D) (XP-D) were used to investigate whether DNA repair pathways were modulated during the cell cycle. Two criteria were used: (1) unscheduled DNA synthesis (UDS) in the presence of hydroxyurea (HU) after exposure to UV light or after exposure to N-acetoxy-acetylaminofluorene (N-AcO-AAF) to quantitate nucleotide excision repair or UDS after exposure to methylmethane sulfonate (MMS) to measure base excision repair; (2) repair replication into parental DNA in the absence of HU after exposure to UV light. Nucleotide excision repair after UV irradiation was induced in WI-38 fibroblasts during cell cycle reaching a max in cultures exposed 14-15 hr after cell stimulation. Similar results were observed after exposure to N-AcO-AAF. DNA repair was increased 2-4 fold after UV exposure and was increased 3-fold after N-AcO-AAF exposure. In either instance nucleotide excision repair was sequentially stimulated prior to the enhancement of base excision repair which was stimulated prior to the induction of DNA replication. In contrast XP-D failed to induce nucleotide excision repair after UV irradiation at any interval in the cell cycle. However, base excision repair and DNA replication were stimulated comparable to that enhancement observed in WI-38 cells. The distinctive induction of nucleotide excision repair and base excision repair prior to the onset of DNA replication suggests that separate DNA repair complexes may be formed during the eucaryotic cell cycle. (Author abstract) (31 Refs)

39. CYTOLOGICAL EVIDENCE FOR DNA CHAIN ELONGATION AFTER UV IRRADIATION IN THE S PHASE.

Minka DF, Nath J
Dept. Medical Genetics, Sch. Medicine, Indiana Univ., Indianapolis, IN
Biochem Genet; 19(3/4):199-210 1981

Human xeroderma pigmentosum cells of the XP12BE (XP classic) excision deficient and XP4BE (XP variant) excision proficient cell lines were studied. Cells were synchronized and 1 mM caffeine added. Six sets of plates were irradiated with UV at 0, 1, 2, 3, 4, and 5 hr during S phase. Six hr after the start of S phase, caffeine was removed from the medium. One plate from each set was labeled with 3H-thymidine (3H-TdR) at 0, 0.5, and 1.5 hr after caffeine removal. Controls consisted of untreated cultures and cultures treated with caffeine or UV. XP classic cells with caffeine had greater 3H-TdR incorporation than cells without caffeine when irradiated at the beginning of S phase. Incorporation of the label declined to non-caffeine levels at the end of S phase. Caffeine did not affect labeling in XP variant cells. Human cells irradiated with UV synthesize lower mol wt DNA than unirradiated cells, due to gaps in the DNA. Repair mechanisms eliminate these gaps within a few hr after irradiation. Results of this experiment indicate occurrence of unscheduled DNA synthesis, possibly chain elongation, during the G2 phase in excision deficient cultures. (30 Refs)

40. BROMODEOXYURIDINE PHOTOLYSIS ASSAY AS A POTENTIALLY USEFUL METHOD FOR ASSESSING DNA DAMAGE AND ITS REPAIR INDUCED BY ULTRAVIOLET LIGHT.

Yatani R, Konishi T, Kusano I, Shiraishi T, Noda M, Ohashi S, Suzuki M
Dept. Pathology, Mie Univ. Sch. Medicine, Tsu, Japan
Mie Med J; 30(3):267-272 1981

The bromodeoxyuridine (BrdUrd) photolysis assay was used to assess DNA damage and repair induced by UV light in three melanoma cell lines, xeroderma pigmentosum (XP), normal human fibroblasts, and HeLa S3 cells. The cells were incubated with 3H-thymidine or 14C-deoxythymidine for 24 hr, incubated in nonradioactive medium for 2 hr, then exposed to 20 Jm-2 of a 254 nanometer (nm) UV light. The cells were then incubated for 24 hr in medium containing hydroxyurea and BrdUrd or deoxythymidine. BrdUrd incorporated into DNA during the repair period by exposing the cell suspension to a 313 nm light. Postreplication repair assays were also conducted. In normal cells, a UV-induced lesion in the DNA was necessary before incubation in BrdUrd synthesized DNA to 313 nm radiation and a UV-induced lesion resulted in the incorporation of BrdUrd throughout the 3H-thymidine cellular DNA. In XP cells, the incorporation of BrdUrd into the DNA after UV-irradiation was negligible. The marked decrease in sedimentation rate seen in normal human fibroblasts after UV, BrdUrd treatment, and 313 nm irradiation did not occur in XP cells although slight differences in XP cells subjected to such treatment were seen compared with those not UV-irradiated. Normal cells became highly sensitive to 313 nm light when they were permitted to repair UV-induced lesions in the presence of BrdUrd, while XP cells did not have that sensitivity, presumably because they cannot make the initial strand breaks which necessarily precede the incorporation of BrdUrd. This assay detects excision repair as a cumulative process and estimates the patch size involved in repair replication as well as interpatch distances. (26 Refs)

41. SENSITIVITY OF EXCISION REPAIR IN NORMAL HUMAN, XERODERMA PIGMENTOSUM VARIANT AND COCKAYNE'S SYNDROME FIBROBLASTS TO INHIBITION BY CYTOSINE ARABINOSIDE.

Cleaver JE
Lab. Radiobiology, Univ. California, San Francisco, San Francisco, CA, 94143
J Cell Physiol; 108(2):163-173 1981

The effects of cell type, cell cycle stage, deoxycytidine pool sizes, concentration of 1-beta-D-arabinofuranosylcytosine (ara-C), and the structure of the aborted repair patch on inhibition of excision repair by ara-C were studied. Primary human cells were obtained by skin biopsy from normal, xeroderma pigmentosum (XP) variant, and Cockayne's syndrome humans. Parental DNA was labeled by growth in 14C-thymidine for at least two to three generations. S-phase cells were labeled with 3H-thymidine. Cultures were then exposed to UV, 13 joules/square meter, with a 5 hr incubation time. With or without hydroxyurea (HU), ara-C inhibited repair of UV damage and resulted in the accumulation of single-strand breaks in DNA during the G1 and G2 phases. The S-phase was resistant to ara-C inhibition, apparently because of either the presence of a pool of deoxycytidine nucleotides during S-phase or the changing roles of different DNA polymerases. Normal and Cockayne's syndrome cells showed similar numbers of breaks, with XP variant cells slightly higher. The number of breaks increased with increasing concentrations of ara-C. HU, when added to ara-C, extended the inhibition into the S-phase. The results suggest that repair proceeds so that both the damaged segment and the repair patch remain attached to the larger DNA strand. Digestion of DNA with exonuclease III indicated that the size of the patch is about 100 nucleotides. (48 Refs)

EFFECTS OF EXOGENOUS AGENTS ON CHROMOSOMES

42. NEW CONCEPTS IN NUTRITION AND CANCER: IMPLICATIONS FOR FOLIC ACID.

Butterworth CE
Dept. Nutrition Sciences, Univ. Alabama, Birmingham, AL, 35294
J Dent Child; 48(4):300-303 1981

Many of the proposed mechanisms by which diet and nutrition may be related to cancer seem to involve a genetic or chromosomal injury that may be conditioned by nutritional factors such as folic acid (FA). Hormone-induced localized nutrient deficiency has been postulated as a mechanism involved in the development of cervical dysplasia in women taking oral contraceptives (OCs). In a clinical trial, FA supplementation led to the regression of OC-induced cervical dysplasias in women who continued to take OCs. No such regression occurred in placebo-treated women, some of whom developed carcinoma in situ. The concept of nutritionally dependent fragile sites and somatic mutations on human chromosomes is not supported by clear evidence that chromosomal fragility is involved in carcinogenesis. However, a combination of chromosomal fragility and deficiencies of FA or another essential nutrient may account for specific mutations in target tissues. One published report describes 34 cases of serious hematologic disease (including 5 acute leukemias) in a family with an inherited defect of cellular FA uptake. Cervical cancer is circumstantially linked to a DNA virus (herpesvirus), and several RNA viruses are known to be oncogenic in animals. The retroviruses induce RNA-directed DNA synthesis via reverse transcriptase. There is good reason to suspect that FA-containing coenzymes play an important role in this DNA synthesis, as they do elsewhere. Folacin plays an important role in the infection of Escherichia coli by T-even bacteriophages. FA and its analogs may play a similar role in viral oncogenesis. (17 Refs)

43. THE ROLE OF GENETIC TOXICOLOGY IN A SCHEME OF SYSTEMATIC CARCINOGEN TESTING.

Williams GM, Weisburger JH, Brusick D
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
ACS Symp Ser; 160:57-87 1981

No single test has been developed for detecting all hazardous chemicals. It is therefore important to formulate the criteria for selecting the best combination of tests for a test battery. A battery should combine detection and confirmation of a hazard in one step. It should be capable of including all types of hazards. The tests should have clear biological significance and should maximize metabolic parameters. The Decision Point Approach involves five sequential steps in evaluating the carcinogenic potential of a chemical. First the structure of the chemical is determined. Then a series of in vitro short-term tests are run. These tests include bacterial mutagenesis, DNA repair, mammalian mutagenesis, sister chromatid exchange, and cell transformation. The evidence provided by the tests is evaluated. A suspected chemical is tested in limited in vivo assays for skin tumor induction in mice, pulmonary tumor induction in mice, breast cancer induction in female Sprague-Dawley rats, and altered foci induction in rodent liver. Further evaluation is made. Chronic bioassays complete the series of tests. A final evaluation of all the tests is made, allowing a decision to be made on the hazard of the chemical in question. (63 Refs)

44. PESTICIDES: MUTAGENIC AND CARCINOGENIC POTENTIAL.

Waters MD, Nesnow S, Simmon V, Mitchell AD, Jorgenson TA, Valencia R
Genetic Toxicology Div., Health Effects Res. Lab., United States Environmental Protection Agency, Research Triangle Park, NC, 27711
ACS Symp Ser; 160:89-113 1981

A phased approach has been developed for evaluating the mutagenic and carcinogenic potential of chemicals. The method combines cost-effective use of limited testing facilities with protection from hazards to human health. Since no single test is capable of detecting all hazardous chemicals, proper testing requires the minimum number of tests which will effectively reveal mutagenic and carcinogenic properties. Phase I involves detection. Short-term bioassays emphasize point mutations and primary DNA damage in species and chromosomal changes in mammalian cells. Phase II tests are used to confirm the results of Phase I. More expensive tests use narrower and more definitive bioassays in cultures, plants, insects, and mammals. Chemicals are tested for both mutagenicity and carcinogenicity. Phase III assesses the risk involved with a chemical. Whole-animal bioassays are used to determine quantitative hazards. Within Phases I and II a 'core battery' of tests is used to indicate a probable negative result, thus eliminating unnecessary testing. The phased approach has been used to test 38 pesticides. The results are discussed as an illustration of how the method works. (71 Refs)

45. IMPROVED MUTAGEN-TESTING SYSTEMS IN MICE. PROGRESS REPORT 1, SEPTEMBER 1979-30 OCTOBER 1980.

Roderick TH
Jackson Lab., Bar Harbor, ME
Improved Mutagen-Testing Systems in Mice. Progress Report 1, September 1979-30 October 1980. Available from National Technical Information Service, Springfield, VA, as DOE/EU/03267-18:, 12 pp., 1981.

Work is continuing on chromosomal inversions and Robertsonians, cytology of inversions, translocations, mutagen test validation, meiotic pairing, and the characterization of induced lethals. (Author abstract)

46. CHROMOSOMAL ANALYSIS IN VINYL CHLORIDE EXPOSED WORKERS: COMPARISON OF THE STANDARD TECHNIQUE WITH THE SISTER-CHROMATID EXCHANGE TECHNIQUE.

Anderson D, Richardson CR, Purchase IF, Evans HJ, O'Riordan ML
Central Toxicology Lab., Imperial Chemical Industries, Ltd., Alderley Park, Macclesfield, Cheshire SK10 4TJ, England
Mutat Res; 83(1):137-144 1981

Twenty-one workers exposed to vinyl chloride (VC) and six controls were subjected to conventional chromosomal analysis

(CA) and the determination of sister-chromatid exchanges (SCE). In addition, SCE in human lymphocytes were studied before and after exposure to gaseous VC in vitro. These workers had been subjected to studies 18 mo before. In the exposed workers the av of the different types of abnormalities were significantly increased with CA, while only a slight, nonsignificant, increase of SCE was noted in the exposed group compared with the controls. In lymphocyte cultures exposed to VC during G0/early G1, and late G1/early S phase, no increase in SCE was noted without metabolic activation; a marked decrease was noted with activation and this was independent of cell cycle phase. The small increases of SCE in workers were attributed to low exposures rather than the inability of VC to induce SCE in human lymphocytes; the SCE levels could have returned to normal relatively quickly after exposure. It is suggested that SCE analysis might not be of much value after very low chronic chemical exposures, but might be useful during high chronic chemical exposures and during the first few days after acute exposure. (19 Refs)

47. CHROMOSOME ANALYSES OF NURSES HANDLING CYTOSTATIC AGENTS.

Waksvik H, Klepp O, Brogger A
Norsk Hydro's Inst. Cancer Res., Montebello, Oslo 3, Norway
Cancer Treat Rep; 65(7/8):607-610 1981

A cytogenetic study of 10 nurses handling cytostatic agents (av exposure, 2,150 hr) and 10 female hospital clerks revealed an increased frequency of chromosome gaps and a slight increase in sister chromatid exchange frequency among the nurses. The increase may be due to exposure to cytostatic drugs and points to these agents as a possible occupational health hazard. A second group of 11 nurses handling cytostatic agents for a shorter period of time (av exposure, 1,078 hr), and three other groups (8 nurses engaged in therapeutic and diagnostic radiology, 9 nurses engaged in anesthesiology, and 7 nurses in a postoperative ward) did not differ from the office personnel, except for an increased frequency of chromosome gaps in the radiology group. (Author abstract) (27 Refs)

48. ACTION OF VARIOUS PHARMACOLOGICAL AGENTS ON THE NUCLEAR AND CHROMOSOMAL STRUCTURES OF HUMAN LYMPHOCYTES.

Bastide P, De Rocca Serra MF, Fellmann N, Jaffray JY, Geneix A, Malet P, Turchini JP
Laboratoire de Chimie Biologique et de Pharmacodynamie, U.E.R. de Pharmacie, 28, place Henri-Dunant, 63001 Clermont-Ferrand Cedex, France
Cytologia (Tokyo); 46(1):387-391 1981

The effects of nine antitumoral agents (alkylating agents: nitrogen mustard, chlorethazine, cyclophosphamide (CP), and ifosfamide (IF); alkylating antibiotics: mitomycin C (MC) and actinomycin D (AD); nucleic acid inhibitors: 5-bromodeoxyuridine (5-BD) and cytarabine (Ara C); alkaloids: teniposide (TP); and others: amikelline (AK)) on nuclear and chromosomal structures were studied in human lymphocytes. TP blocked entrance into prophase, caused nuclear polymorphism, and produced thickening of chromatid strands. 5-BD and Ara C, and to a less degree MC, induced secondary chromosomal stretching and constriction. AD, CP, IF, and Ara C produced chromatid unwinding. MC and AD, and to a lesser extent 5-BD and Ara C, produced chromosomal gaps and breaks. The effects of AK on the lymphocyte nucleus are described. (7 Refs) (In FRE)

49. EFFECTS OF ACUTE AND CHRONIC ADMINISTRATION OF MITOMYCIN C ON THE INDUCTION OF SISTER CHROMATID EXCHANGES IN VIVO.

Kram D, Bynum GD, Dean R, Schneider EL, Farland WH, Williams JR
Dept. Radiology, George Washington Univ. Sch. Medicine, Ross Hall 113, 2300 I St ., NW, Washington, DC, 20037
Environ Mutagen; 3(4):489-495 1981

The relationship between the timing of mutagen administration, sister chromatid exchange (SCE) induction, and persistence of SCE-inducing lesions was examined using bone marrow cells from male C57BL/6J mice in vivo as the cell system and mitomycin C (MMC) as the mutagenic agent. Administration of MMC (2.5 mg/kg) 1, 6.5, and 13 hr after the onset of bromodeoxyuridine (BrdU) infusion resulted in the induction of approx 45 SCE/cell at each time point. When MMC was injected 19.5 hr after the onset of BrdU infusion, SCE levels averaged approx 17 SCE/cell. When MMC was injected 26 hr prior to BrdU infusion, only baseline levels of SCE were detected. Administration of MMC 19.5 hr prior to BrdU infusion resulted in a small but significant induction of SCE. When MMC was given 6.5 hr before BrdU labeling, an av of 25 SCE/cell was seen. Following chronic weekly or bimonthly injections involving large accumulated doses (up to 15 mg/kg), SCE levels in the treated mice were not significantly different from controls, although high MMC doses did significantly impair cell replication kinetics. The results indicated that nondividing cells are capable of removing few if any MMC-induced lesions that can result in SCE formation. However, one round of DNA replication appears to be sufficient to remove most or all MMC-induced lesions that may lead to SCE formation. (19 Refs)

50. INDUCTION OF 8-AZAGUANINE RESISTANCE AND SISTER CHROMATID EXCHANGE IN HUMAN LYMPHOCYTES EXPOSED TO MITOMYCIN C AND X RAYS IN VITRO.

Evans HJ, Vijayalaxmi
Medical Res. Council, Clinical and Population Cytogenetics Unit, Western General Hosp., Edinburgh EH4 2XU, Scotland
Nature; 292(5824):601-605 1981

Indirect evidence implies that 8-azaguanine-resistant (AGr) lymphocytes in human peripheral blood are mutants associated with the loss of the hypoxanthine-guanine phosphoribosyltransferase (HPRT) locus on the active X chromosome, the mutation frequency increasing linearly with age. AGr variants are readily induced in lymphocytes exposed to mitomycin C in vitro, their incidence correlating with induced sister chromatid exchanges (SCEs). Although SCE events and the development of an AGr phenotype may reflect a common type of DNA damage, mitomycin C-induced AGr variants are not mutants but are suggested to be cells having a transcriptional block at the HPRT locus. AGr variants are also readily induced by x-rays in vitro, their incidence correlates closely with the incidence of aberrations induced in the X chromosome and they are considered to have a mutational origin. (Author abstract) (38 Refs)

51. OBSERVATIONS ON THE EFFECT OF X-RAY ALONE AND IN COMBINATION WITH ULTRASOUND ON HUMAN CHROMOSOMES.

Kunze-Muhl E
Institut fur Allgemeine Biologie der Medizinischen Fakultat, Universitat Wein, S chwarzpanierstrasse 17, A-1090 Wien, Austria
Hum Genet; 57(3):257-260 1981

The synergistic effect between ultrasound (US) and ionizing radiation was studied in human peripheral blood lymphocytes. Blood samples were treated with US before or after exposure to x rays (50, 100 or 200 R). The samples were cultured, and the frequency of chromosome aberrations was determined. The yield of chromosome aberrations was found to depend upon the dose, duration, and order of treatment: 10-min exposure to high intensity US before x rays increased the incidence of all types of aberrations, while 10-min exposure to high intensity US after x- rays decreased the yield of minutes and fragments. One-hr exposure to low intensity US after irradiation with 200 R decreased the frequency of chromosome aberrations, compared with significant increase of the frequency of chromosome aberrations recorded in case of 1-hr exposure to low intensity US before irradiation with 200 R. (28 Refs)

52. ASPECTS OF ENVIRONMENTAL RADIATION AND DOSIMETRY CONCERNING THE HIGH BACKGROUND RADIATION AREA IN CHINA.

High Background Radiation Research Group
(c/o W. Luxin) Lab. Industrial Hygiene, Ministry Public Health, 2 Xinkang Street, Peking, People's Republic of China
J Radiat Res (Tokyo); 22(1):88-100 1981

The study of the health status of residents of Yangjiang County, Guangdong Province, China, an area where the radiation level is about three times that of neighboring areas, is reported. Between 1972 and 1979 no significant difference was observed between high background and control areas with regard to detrimental effects, except perhaps chromosome aberrations. Chemical and gamma-ray spectrometric analyses of the contents of radionuclides in control and high background areas indicated that natural radionuclides were in normal ranges in the former areas while increased by factors of five for uranium and radium and 6-7 for thorium in the latter area. Environmental radiation exposure rates in the high background area fluctuated from 15 to 64 microrads (uR)/hr in the fields, and from 32 to 140 uR/hr in the rooms, as compared with control areas where the values were 5-17 uR/hr in the field and 10-56 uR indoors. The daily intake and localization of radionuclides were determined. 222-Radon and 220-radon activities were determined in exhaled breaths. 228-Radium levels in human teeth were also analyzed. Radiation doses to bone marrow and bone surfaces were estimated. (7 Refs)

53. BIOLOGICAL EFFECTS OBSERVED IN MAMMALS MAINTAINED IN AN AREA OF VERY HIGH NATURAL RADIOACTIVITY.

Leonard A, Delpoux M, Chameaud J, Decat G, Leonard ED
Lab. Mammalian Genetics, Dept. Radiobiology, C.E.N.-S.C.K., B-2400 Mol, Belgium
Can J Genet Cytol; 23(2):321-326 1981

Male rabbits (Oryctolagus cuniculus) were maintained for a 28-mo period on the f loor of a hut built at a site in southwestern France where the dose rate from natural radioactivity amounts to about 8 mrad/h. Male and female BALB/c mice (Mus musculus) were also placed in the hut during the summer period. The observations performed on those animals demonstrate that exposure to high natural radiation can increase the frequency of chromosome aberrations in somatic cells and indicate also that fertility in males and females is affected in an inverse manner. Model experiments with radon exposure of laboratory rabbits under controlled conditions have shown that the chromosome aberrations observed in somatic cells are not due to the radon exposure but essentially to gamma irradiation. (Author abstract) (23 Refs)

54. ONCOGENIC ACTION OF BETA, PROTON, ALPHA AND ELECTRON RADIATION ON THE RAT SKIN.

Burns FJ
Dept. Environmental Medicine, New York Univ., New York, NY
Oncogenic Action of Beta, Proton, Alpha and Electron Radiation on the Rat Skin. Available from National Technical Information Service, Springfield, VA, as COO-3380-33:, 29 pp., 1981.

Rat skin is being utilized as an empirical model for testing dose and time related aspects of the oncogenic action of ionizing radiation, UV light, and polycyclic aromatic hydrocarbons. Molecular lesions in the skin DNA, including strand breaks and thymine dimers, are being measured and compared to tumor induction. The induction and repair kinetics of molecular lesions are being compared to split dose repair. Modifiers and radiosensitizers are being utilized to test specific aspects of a chromosome breakage theory of radiation oncogenesis. (Author abstract)

55. THE MODULATING EFFECT OF RETINOIDS AND A TUMOR PROMOTER ON MALIGNANT TRANSFORMATION, SISTER CHROMATID EXCHANGES, AND NA/K ATPASE.

Borek C, Miller RC, Geard CR, Guernsey D, Osmak RS, Rutledge-Freeman M, Ong A, Mason H
Radiological Res. Lab., Dept. Radiology, Cancer Center/Inst. Cancer Res., Coll. Physicians and Surgeons, Columbia Univ., New York, NY, 10032
Ann NY Acad Sci; 359:237-250 1981

The interactions between retinoids and tumor promoting compound 12,O-tetradecanoyl-phorbol 13-acetate (TPA) were studied in mouse heteroploid C3H/10T1/2 cells and in diploid hamster embryo cells. TPA added to the culture medium immediately after irradiation with x-rays (300 rads) enhanced markedly the yield of transformed cells, while incubation with retinoids reduced the transformation rate. Retinoids were able to eliminate in an irreversible manner the promoting effect of TPA. Both retinoids and TPA had a comparatively negligible effect on the frequency of sister chromatid exchange. In both cell lines, retinoids reduced the level of Na/K ATPase, while TPA enhanced activity of the enzyme; simultaneous exposure to retinoids and TPA resulted in the normalization of the enzyme level. (38 Refs)

56. GENOTOXICITY OF N-METHYL-N-NITROSOUREA IN THE PRESENCE OF AMPHOPHILIC MEMBRANE-ACTIVE COMPOUNDS.

Stahl KW, Cheng S-J, Bayer U, Chouroulinkov I
Pathologisches Institut der Universitat Freiburg, 19, Albertstrasse, D-7800 Freiburg, W. Germany
Toxicol Appl Pharmacol; 60(1):16-25 1981

Genotoxicity of N-Methyl-N-nitrosourea (NMU) was measured in vitro in V79 Chinese hamster lung fibroblasts, and in vivo in home-bred Chinese hamsters. NMU was administered in the presence of the sister chromatid marker 5-bromodeoxyuridine (BrdU) and in the presence of the amphophilic, membrane-active compounds n-octanol, Cremophor EL, and 2-(2-methoxyethoxy)ethyl-8-(cis-2-n octylpropyl)octanoate (A2C), according to varying time schedules. Genotoxicity was measured by the occurrence of sister chromatid exchange (SCE). NMU and BrdU together had a significant effect on SCE In Vitro that was not detectable In Vivo. NMU induced dose-dependent SCE frequencies in V79 cells. Pretreatment of V79 cells with the membrane-active compounds reduced the frequency of NMU-induced SCE. Both cell-integrated and extracellular Cremophor EL reduced NMU genotoxicity. The inhibition effect of Cremophor EL was greater in vivo than in vitro. The results seem to indicate that the amphophilic, membrane-active compounds reduce the genotoxicity of NMU by reducing its bioavailability in the cell nucleus. This is done apparently by increasing the number of nucleophilic sites in the cell membrane, which compete for the NMU molecules. (18 Refs)

57. LACK OF MUTAGENIC EFFECTS OF HALOTHANE IN MAMMALS IN VIVO.

Basler A, Rohrborn G
Inst. Human Genetics and Anthropology, Univ. Duesseldorf, Universitatsstr. 1, Gebaude 23.12, D-4000 Dusseldorf, W. Germany
Anesthesiology; 55(2):143-147 1981

Rodents were exposed in vivo to various clinical doses of halothane to observe structural chromosome aberrations, micronuclei, sister chromatid exchanges (SCEs), dominant lethal mutations, and interferences with phases of the cell cycle. The frequency of chromosome aberrations in bone marrow cells was not increased after exposing Chinese hamsters to 1% halothane once for 3 hr, twice for 3 hr (exposures 24 hr apart), or to 0.5% for 24 hr. The analysis of SCEs in bone marrow cells were also negative after exposing hamsters to 1% halothane for 3 hr, or to 0.5% for 12 hr. In halothane-exposed female mice (0.75% for 16 hr), oocyte maturation (meiotic stages) was delayed. Another group of exposed female mice (1% for 5 hr) were mated with untreated males. The number of dead implants was not increased as compared to controls. In liver cells of 16-day-old living embryos, neither monosomic nor trisomic cells were observed. Male mice were exposed to 1% halothane for 1 hr per day for 48 days. On the evening of the 48th they were mated with untreated females. Dominant lethal mutations were not increased as compared to controls. In RBC of these chronically exposed male mice, the frequency of micronuclei was not significantly enhanced. The authors conclude that halothane does not induce mutations under the in vivo conditions tested in this study. (Author abstract) (21 Refs)

58. DIETHYLSTILBESTROL-DIPHOSPHATE INDUCES CHROMOSOMAL ABERRATIONS BUT NOT SISTER CHROMATID EXCHANGES IN MURINE BONE MARROW CELLS IN VIVO.

Ivett JL, Tice RR
(c/o Tice) Medical Dept., Brookhaven Natl. Lab., Upton, NY, 11973
Environ Mutagen; 3(4):445-452 1981

The ability of diethylstilbestrol (DES) to induce both chromosomal aberrations and sister chromatid exchanges (SCEs) and to influence cellular proliferation kinetics was studied. The reported ability of DES to induce aneuploidy in bone marrow cellular populations of both male and female C57B1/6J mice was examined. The female mice clearly demonstrated a dose-dependent increase in chromatid-type aberrations, though no increase in SCE frequencies was observed at any dose of diethylstilbestrol diphosphate (DES-dp). Significantly fewer achromatic lesions (13.6 versus 54.0%) and deletions (5.2 versus 13.0%) were induced in males than in females at 100 mg/kg DES-dp. At a dose of 200 mg/kg, cellular proliferation was limited to one generation in female mice, while 32% of cells in equally exposed male mice divided at least twice. Ovariectomy reduced both the ability of DES-dp to inhibit cellular proliferation and the high degree of variability between animals at high DES-dp doses. The results of aneuploidy studies failed to support the conclusion that DES induces aneuploidy in either sex. The results indicated that DES is a clastogenic agent in vivo which may relate to its carcinogenicity. (23 Refs)

59. EVALUATION OF THE GENETIC ACTIVITY OF INDUSTRIALLY PRODUCED CARBON BLACK.

Kirwin CJ, LeBlanc JV, Thomas WC, Haworth SR, Kirby PE, Thilagar A, Bowman JT, Brusick DJ
Phillips Petroleum Co., B-57 AB, Bartlesville, OK, 74004
J Toxicol Environ Health; 7(6):973-989 1981

The mutagenic potential of a single sample of oil furnace, N-339 carbon black (NCB), was studied in five assays. In the Salmonella assay, NCB did not cause significant increase in the reversion index of any of the tester strains with or without metabolic activation by rat liver microsomes. Three of the six dose levels of NCB were associated with statistically significant increases in sister chromatid exchange frequencies, but these appeared to be due to the slightly lower than normal frequency in the solvent culture medium. Cellular toxicity was exhibited in the nonactivated system for the mouse lymphoma assay at 50,000 ug/ml NCB. The activated system exhibited cellular toxicity at 10,000 ug/ml. At 50,000 ug/ml both systems produced at least 99% cell death. Over a wide range of concentrations, NCB did not induce any significant increase in mutant frequencies in the L5178Y mouse lymphoma assay. The cell transformation assay showed the desired cellular toxicity of more than 50% reduction in relative cloning efficiency with NCB. A dose of 16,384 ug/ml NCB reduced relative cloning efficiency to 38%. In the C3H/10T1/2 cell transformation assay, NCB did not cause morphological transformation of cells, while the positive control, dimethylbenzanthracene, exhibited the expected positive results. In the Drosophila assay, designed to detect point mutation, NCB did not induce significant genetic damage under test conditions. The results indicated that NCB does not exhibit any significant genetic activity in the five short-term genetic activity assays performed. (40 Refs)

60. SISTER CHROMATID EXCHANGE FREQUENCY IN MOUSE EMBRYO CHROMOSOMES FOLLOWING IN UTERO EXPOSURE TO BETA-AMINOPROPIONITRILE.

Salo DF, Martino LJ, Tucci SM
Dept. Anatomy, Albany Medical Coll. and Birth Defects Inst., Albany, NY, 12208
Arch Toxicol; 47(4):305-310 1981

The effects of the teratogenic drug beta-aminopropionitrile (BAPN) on the induction of sister chromatid exchanges (SCEs) in utero was evaluated. The frequency of SCEs exchanges increased with increasing doses of BAPN in the day 10 mouse embryo. The present study warns of the possible clastogenic activity of BAPN. (Author abstract) (16 Refs)

61. CYTOGENETIC ANALYSIS OF TRANSLOCATIONS INDUCED BY THE CHEMICAL MUTAGEN THIOTEPA IN SPERMATIDS OF MALE MICE.

Malashenko AM, Goetz P

Scientific Res. Lab. of Experimental Biological Models, Academy of Medical Sciences of the U.S.S.R., Moscow, USSR

Folia Biol (Praha); 27(3):178-185 1981

Mutagenic action of thioTEPA in germ cells of male mice was investigated with cytogenetic analysis of meiotic cells at diakinesis/metaphase I in F1 hybrid males that were reciprocal translocation heterozygotes. C57BL6/JT (BL6) male mice were injected ip with 1.25 mg/kg body wt of a soln of thioTEPA. The BL6 males were mated to (BALB/cY x DBA/2Y) F1 hybrid females during the second wk after thioTEPA treatment. F1 progeny from this mating came from germ cells treated as late spermatids that are most sensitive to thioTEPA. F1 males (128 total) were derived from matings of 30 treated male parents; 31 of the F1 males were half sterile and 12 were completely sterile. Cytogenetic analysis was carried out in these 43 F1 males. Prevalent types of multivalent configurations were Ring IV in 15 F1 males and Chain IV in 20 males, and 1 male showed the same proportion of cells with chains and rings. It was thought that damage to the ends of chromosomes did not reflect specificity of the effect of certain mutagens, but depended on the intensity of the mutation process. The mutagenic action at which the heterozygote frequency approaches the max possible frequency (approx 30%) was thought to be characterized by a random distribution of breaks along the chromosomes. (15 Refs)

62. CHROMOSOMAL ABERRATIONS AND SISTER-CHROMATID EXCHANGES INDUCED BY GASEOUS NITROGEN DIOXIDE IN CULTURED CHINESE HAMSTER CELLS.

Tsuda H, Kushi A, Yoshida D, Goto F

Central Res. Inst., Japan Tobacco and Salt Public Corp., 6-2 Umegaoka, Midori-ku, Yokohama, Kanagawa 227, Japan

Mutat Res; 89(4):303-309 1981

Cultured Chinese hamster V79-H3 cells were exposed to NO2 gas and NaNO2 at various concentrations. The induction rate of chromosomal aberrations (CA), including chromatid breaks and chromatid exchanges, was 35% at a NO2 gas concentration of 100 ppm. NO2 gas concentrations of 10-50 ppm induced mainly chromatid gaps and breaks; its induction rate of CA was still significant. NaNO2 induced CA significantly at concentrations of 50-100 mM. Sister-chromatid exchanges were significantly increased by NO2 gas in concentrations of 5, 10, 20, 50 and 100 ppm; the enhancing factors were 1.3, 1.7, 1.6, 2.2 and 2.5, respectively. Sister chromatid exchanges were significantly increased by NaNO2 at concentrations of 50 and 100 mM. It is noteworthy that the CA rate was not increased by NO2 gas, even at concentrations of 100 ppm, if the experimental cells were not washed in a balanced salt soln prior to their exposure to the gas. It is therefore assumed that the cells are equipped with protective materials on their surface. (15 Refs)

GENERAL REVIEWS

63. THE CHROMOSOMES IN HEMATOLOGY.

Berger R

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Cancer Genet Cytogenet; 4(1):69-88 1981

Chromosome studies in hematological disorders made rapid and significant advances following the introduction of banding techniques, and the most salient features of these studies are succinctly reported in this review. Considering the consistency of the chromosome anomalies first, it appears that about 50% of the acute leukemias do not present with or develop detectable karyotypic changes, which could lead to the assumption that they may play a role at any level in the development of the malignant process. More recent work seems to indicate that the normal metaphases found in the marrow by direct methods and on unstimulated blood may not have originated from leukemic cells. If clonal chromosome anomalies are to be of some significance, they ought to be nonrandom in character and that is what studies of the last few yr have shown. Thus, correlations between these chromosomal anomalies and the types of malignant proliferation have been established. Other examples of nonrandom anomalies were found in acute lymphoblastic leukemia (ALL) (deletion of the long arm of chromosome number 6; translocation t(4;11)), in chronic lymphocytic leukemia, certain myeloproliferative syndromes, and in preleukemia (the 5q- anomaly). The relationship between constitutional and acquired chromosomal anomalies (trisomy and acute leukemia), as well as between chromosome breakage syndromes and malignant proliferation, is discussed. Modification of the chromosome changes during the course of the disease have also contributed greatly to our better understanding of these conditions; disappearance of the anomalies during remission and reappearance in relapse of acute leukemia and clonal evolution, allowing critical evaluation of the relationship between the presence of consistent nonrandom chromosome anomalies and prognosis of the disease. Finally, the practical indications for chromsome investigations in hematological disease are listed, and certain future developments are mentioned. (179 Refs)

64. METABOLIC ACTIVATION AND MUTAGENICITY OF 4 VINYLIC MONOMERS (VINYL CHLORIDE, STYRENE, ACRYLONITRILE, BUTADIENE).

Duverger M, Lambotte M, Malvoisin, De Meester C, Poncelet F, Mercier M

(c/o Poncelet) Lab. Biotoxicology, Univ. Louvain Sch. Pharmacy, U.C.L.-73.69, B. 1200 Brussels, Belgium

Toxicol Eur Res; 3(3):131-140 1981

Literature data on the mutagenic activity and metabolism of monomers vinyl chloride (VCM), styrene (STY), acrylonitrile (ACN) and butadiene (BUT) are reviewed. Vinylic monomers were shown to be susceptible to metabolic conversion by the mixed function oxidase of the endoplasmic reticulum into primary reactive intermediates (oxiranes). VCM, STY, ACN, and BUT were mutagenic in Salmonella typhimurium test system. VCM was shown to induce recessive lethals in Drosophila melanogaster. Incubation of Chinese hamster cells with VCM produced a dose-dependent mutagenicity and cytotoxicity. An increased frequency of chromosome aberrations was recorded in workers who had an occupational exposure to VCM and STY. (130 Refs)

65. REVIEW ARTICLE. REGULATION OF EXPRESSION OF THE INTEGRATED RETROVIRUS GENOME.

Weinberg RA, Steffen DL
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
J Gen Virol; 54(part1):1-8 1981

The phenomena of regulation which control expression of the integrated provirus at the level of transcription are surveyed. Topics discussed include (1) the regulation of transcription of endogenous proviruses, which derive from those retrovirus genomes carried as genetic determinants in the germ lines of many vertebrates, (2) differential expression of endogenous (generally tightly suppressed) and exogenous proviruses introduced by horizontal spread, (3) cis-acting control of provirus expression, in which ex pression of endogenous but not exogenous proviruses is repressed in the same cell, (4) mechanisms of interaction between proviruses and neighboring cellular elements, where provirus activity depends strongly upon the chromosomal environment (perhaps chromatin configuration), (5) trans-acting control mechanisms in which activation of expression is mediated by diffusible intracellular factors (perhaps cellular proteins associated with steroid receptors), and (6) molecular models of control. (37 Refs)

OTHER RELATED STUDIES

66. FINE NEEDLE ASPIRATION BIOPSY: A USEFUL TOOL IN TUMOR CYTOGENETICS WITH SPECIAL REFERENCE TO MALIGNANT LYMPHOMAS.

Kristoffersson U, Olsson H, Mark-Vendel E, Mitelman F
Dept. Clinical Genetics, Univ. Hosp., S-221 85 Lund, Sweden
Cancer Genet Cytogenet; 4(1):53-60 1981

A method for chromosome analysis of malignant cells by means of fine needle aspiration biopsy has been developed. The method has some obvious advantages compared to conventional surgical biopsy. During a 1-yr period 25 consecutive non-Hodgkin, non-Burkitt lymphoma biopsies from 19 patients have been studied. In 14 out of 21 lymph node biopsies chromosome analysis was successful; whereas, 4 biopsies of sc lymphomas were unsuccessful. (Author abstract) (5 Refs)

67. REPLICATION OF SIMIAN VIRUS 40 DNA IN NORMAL HUMAN FIBROBLASTS AND IN FIBROBLASTS FROM XERODERMA PIGMENTOSUM.

Ozer HL, Slater ML, Dermody JJ, Mandel M
Dept. Biological Sciences, Hunter Coll., City Univ. New York, New York, NY, 10021
J Virol; 39(2):481-489 1981

Simian virus 40 infection of semipermissive human diploid fibroblasts (HF), at early passage in cell culture, was compared with that of permissive established monkey cell lines. Viral DNA can be readily detected at 24 to 48 hr postinfection at 37 C with a high multiplicity of infection, approaching 10% of that of monkey cells (TC7). The length of time necessary for replication of an av molecule of viral DNA was found to be indistinguishable in HF and TC7 cells. Strand elongation plus termination were assessed by following the accumulation of DNA I at 40 C from replicative intermediates of tsA30 prelabeled at 33 C, obviating isotope pool problems. Combined initiation and elongation of wild-type viral DNA was measured by density shift experiments involving a 5-bromodeoxyuridine chase of prelabeled [3H]thymidine-labeled viral DNA. Determination of accumulation of viral T and V antigens supports the conclusion that the most likely basis for the reduced virus yield in HF cells results from the inefficiency of an early stage in virus infection, before or during uncoating. Similar results were obtained in fibroblasts derived from patients with xeroderma pigmentosum, suggesting that enzymes of uv repair are not required in unirradiated simian virus 40 DNA synthesis. (Author abstract) (34 Refs)

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HE 20.3173/2:

CLINICAL STUDIES OF CHROMOSOMES IN HUMAN CANCER

1. PHILADELPHIA-POSITIVE ACUTE LEUKEMIAS AS APPARENTLY 'EX NOVO' HEMATOLOGIC PHENOMENA. TWO CASE REPORTS.

Sanchez-Fayos J, Outeirino J, Calabuig T, Benitez J, Paniagua C, Serrano D, Paniagua G
Departamento de Hematologia, Universidad Autonoma, Facultad de Medicina, Madrid, Spain
Rev Clin Esp; 161(5/6):323-326 1981

Philadelphia chromosome (Ph1) was found in two acute leukemia cases: one acute myelogenous leukemia (AML) and one acute lymphoblastic leukemia (ALL). The patients (female, respectively 14 an d 25 yr old) had short prediagnostic histories. The former died on day 3 of chemotherapy treatment. The latter had complete remission for 2 mo after chemotherapy, but recurrence and sepsis resulted in death. In both cases cytogenetic study showed a mosaic Ph1+/Ph1-. In AML 30% of metaphases had karyotype 46XX, Ph1+. In ALL, studied during relapse, 17% of metaphases had karyotype 48XX, Ph2+,Ph1+, +3; 13% had an extra chromosome of pair 17. Acute Ph1+ leukemias may represent different biological phenomena; the possibilities are discussed. (27 Refs) (In SPA)

2. CHROMOSOME ANALYSIS IN BONE MARROW LYMPHOCYTES IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA AND PRELEUKEMIA.

Karolyi G, Kosztolanyi Gy, Kajtar P, Molnar S
Gyermekklinika, Pecsi Orvostudomanyi Egyetem, Pecs, Hungary
Orv Hetil; 122(34):2087-2088,2091 1981

Chromosome analyses were carried out in bone marrow and peripheral blood lymphocytes from 19 children with acute lymphocytic leukemia, 11 children with preleukemia (including polycythemia vera and pancytopenia), and from 19 adults with chronic myeloid leukemia. The Philadelphia chromosome and chromosome 1 were affected most frequently. The heterochromatic portion of chromosome 1 was asymmetrically enlarged or reduced in some of the children with leukemia and preleukemia, and pericentric inversion was found in one case. The findings support the general assumption of a relationship between the C band and the development of malignant disease. Correlation was found between the clinical and cytogen[illegible] picture. (11 Refs) (In HUN)

3. CYTOGENETIC FINDINGS IN T-ZO[illegible]

Godde-Salz E, Schwarze EW, Stein H, Le[illegible]
Dept. Human Genetics, Univ. Kiel, Sch[illegible] Germany
J Cancer Res Clin Oncol; 101(1):81-89 19[illegible]

Histologic, immunologic, and cytoge[illegible] ported for five non-Hodgkin's lymphomas [illegible] agnostic criteria of T-zone lymphoma; ie, they co[illegible] the T-region components of lymphoid tissue and also B-re[illegible] remnants. The patients, aged 64-77 yr, included two women and three men. In 4/5 cases, the lymph node architecture was completely effaced, with the exception of the residual B areas (follicles). The B cells were identified immunologically as the nonneoplastic cells, and the cells that formed rosettes with sheep RBC were found to be the tumor cells. The chromosome analyses revealed abnormal clones as well as normal mitoses in four cases. Structural rearrangements involved chromosomes 1, 2, 3, 4, 14, and Y. Some tumors showed the loss of chromosomes 3, 5, 6, or 13 and some a gain of chromosomes 3 and 9. There was a high frequency of structural and numerical aberrations in chromosome 3, but a low frequency of 14q markers in one case. The number of patients was too small to determine whether this pattern is specific for the T-zone lymphomas. (21 Refs)

4. CHROMOSOME STUDIES IN ADULT T-CELL LEUKEMIA IN JAPAN: SIGNIFICANCE OF TRISOMY 7.

Ueshima Y, Fukuhara S, Hattori T, Uchiyama T, Takatsuki K, Uchino H

Dept. Medicine, Box 420, Univ. Chicago, Chicago, IL, 60637

Blood; 58(3):420-425 1981

Chromosomes were studied in cells from 15 Japanese patients with adult T-cell leukemia (ATL). Mitoses were obtained from unstimulated peripheral blood in 12 patients and a lymph node in 1 patient. In two other patients, mitotic cells were obtained solely from peripheral blood stimulated with phytohemagglutinin (PHA). Chromosomally abnormal cells were seen in 14 of the 15 patients. The abnormal cells had a modal number of chromosomes in near diploid range in 12 patients, and in near triploid and tetraploid range in the remaining 2 patients, respectively. Eight of the nine patients analyzed by Q-banding had clonal chromosome abnormalities. The most common abnormality was trisomy number 7 or 7q, which was seen in five cases and has been primarily observed in lymphoid neoplasms. A 14q+ marker chromosome was found in two patients and a Dq+ in one patient; loss of a sex chromosome was found in three patients. Most chromosomes were involved in gains, losses, or structural rearrangements, but abnormalities of number 11, which have been frequently found in lymphoid malignancies, was not observed in our series. The significance of these chromosome abnormalities is discussed. (Author abstract) (37 Refs)

5. MALIGNANCY ASSOCIATED WITH CONGENITAL ADRENAL HYPERPLASIA.

Duck SC

[illegible] Endocrinology, 1700 W. Wisconsin Ave., Milwaukee,

[illegible] deficiency adrenal hyper- [illegible] malignant tumor are de- [illegible] from 36 fami- [illegible] HDAH was [illegible] these patients were thriving at the time of report: Patient 2 was disease free; Patient 3 underwent repeated spinal surgery for tumor regrowth in 1979 and continues to grow along the 25th to 50th percentiles; Patient 4 was responding appropriately after 14-18 scheduled mo of chemotherapy. Patient 3 also had juvenile schizophrenia and trisomy of the proximal segment of the long arm of chromosome 13. The coexistence of neoplasms in children with HDAH is discussed. (9 Refs)

DNA CONTENT AND PLOIDY CHANGES ASSOCIATED WITH CANCER

6. THE RELATIONSHIP BETWEEN LYMPHOCYTE NUCLEAR MORPHOLOGY AND CELL CYCLE STAGE IN LYMPHOID NEOPLASIA.

Diamond LW, Weisenburger DD, Rappaport H
Dept. Pathology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Am J Hematol; 11(2):165-173 1981

A significant percentage of lymphoid cells isolated from three lymphoid neoplasms (nodular lymphoma mixed cell type, mycosis fungoides, and Sezary syndrome) had tetraploid or near-tetraploid DNA content, as determined by flow cytometric analysis. In each case, a morphologically distinct population of cells with large, irregular nuclei was present, the percentage of which corresponded to the percentage of tetraploid cells. In a fourth case (diffuse 'histiocytic' lymphoma), cells were sorted on the basis of DNA content from the G0-G1 compartment and compared morphologically to cells sorted from the S-G2 (M) compartment. The G0-G1 cells had clumped nuclear chromatin, lacked prominent nucleoli, and had a mean nuclear diameter of 10.18 +-1.22 um. The sorted cells with S-G2(M) DNA content had one to several prominent nucleoli and less clumped nuclear chromatin, and they were significantly larger, with a mean nuclear diameter of 13.76 +-1.59 um (p less than 0.00001). These preliminary results suggest that, in lymphoid malignancies, certain morphologic characteristics of individual lymphoid cells are related to their DNA content (level of ploidy) and/or the stage of the cell within its division cycle. (Author abstract) (18 Refs)

7. ISOLATION AND CHARACTERIZATION OF POLYPLOID NUCLEI OF R3230AC MAMMARY ADENOCARCINOMA AND COMPARISON WITH NORMAL MAMMARY NUCLEI.

Kulick D, Liu DK
(c/o Liu) Dept. Pharmacology and Specialized Cancer Res. Center, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Cancer Res; 41(10):3907-3912 1981

The R3230AC mammary adenocarcinoma is biochemically similar to the normal lactating mammary gland in many ways, including the RNA/DNA ratio. However, the tumor differs from normal in important ways, which include having a DNA content 2 to 4x higher than the max value for normal mammary gland. This raises the question of whether the cells of the tumor all have more DNA than normal cells. In order to determine how tumor DNA is distributed and whether its transcriptional activity differs from normal, we have compared the ploidy and RNA polymerase activities of nuclei isolated from both sources. Nuclei were also examined for their content of Ca++-stimulated RNase activity, a marker of mammary differentiation. Sucrose density gradient centrifugation of tumor cell nuclei revealed three nuclear types, designated T1, T2, and T3, representing 25, 48, and 27% of total nuclei isolated. T1, T2, and T3 nuclei contained, respectively, 6.5, 12.3, and 19.0 pg DNA per nucleus, representing diploid, tetraploid, and hexaploid amounts of DNA. Nuclear RNA and protein increased in proportion to ploidy. By contrast, cell nuclei isolated from lactating mammary gland formed only two bands (M1 and M2), comprising 54 and 46%, respectively, of total nuclei isolated. Both M1 and M2 nuclei contained diploid amounts of DNA. Therefore, the higher DNA content in the tumor is attributable, at least in part, to the presence of polyploid nuclei in the majority of tumor cells. The combined activity of DNA-dependent RNA polymerases I, II, and III per nucleus was the same in T1, T2, and T3; M1 and M2 also had activities similar to each other but much lower than the tumor types. Activity attributable to polymerase I (resistant to 200 ug alpha-amanitin per ml), polymerase II (inhibited by 0.06 ug alpha-amanitin per ml), and polymerase III (inhibited by 200 ug alpha-amanitin per ml) was about 35, 50, and 15%, respectively, for each class of tumor nuclei. The corresponding values for M bands were about 44, 34, and 22%. These results suggest that tumor cells synthesize more heterogeneous RNA than do mammary cells of lactating rats, but the latter synthesize more ribosomal RNA. Activity of mammary-specific Ca++-stimulated RNase increased slightly per nucleus as the ploidy of tumor nuclei increased, but in every T group the activity was less than one-half of that of M1 or M2 nuclei. Thus, despite differences in ploidy, all tumor nuclear classes show a lesser degree of differentiation than nuclei from the lactating gland, with respect to their capacity for synthesis of ribosomal RNA compared to messenger RNA and their expression of Ca++-stimulated RNase. (Author abstract) (31 Refs)

8. COMPARISON OF LEIOMYOMA AND LEIOMYOSARCOMA ON THE BASIS OF DNA HISTOGRAMS.

Kimura O, Nishidoi H, Osaki Y, Miyano Y, Adachi H, Kaibara N, Koga S, Hashimoto K
First Dept. Surgery, Tottori Univ. Sch. Medicine, Tottori, Japan
Gan No Rinsho; 27(10):1205-1209,A-57 1981

Nuclear DNA content was measured with a microspectrophotometer in cells from five leiomyomas, four leiomyoblastomas, and two differentiated type leiomyosarcomas of the stomach, and one differentiated-type leiomyosarcoma of the small intestine resected from patients. Percentages of hypertriploid (over 3 c) and hypertetraploid (over 4 c) histograms were determined for each tumor type. Most of the gastric leiomyomas were less than 3 cm in diameter and occurred in the gastric corpus; hypertriploid and hypertetraploid histograms occurred in an av of 13.0% and 5.0%, respectively of the cells. Most of the leiomyoblastomas were greater than 4 cm in diameter and occurred in the gastric corpus or fundus; hypertriploid and hypertetraploid histograms were observed in 34.6% and 22.9%, respectively, of the cells. Hypertriploid and hypertetraploid histograms occurred in an av of 95.5% and 68.9%, respectively, of the leiomyosarcoma cells. On the basis of histograms, diagnosis of leiomyosarcoma was thought to be indicated by hypertriploids occurring in greater than 50% of histograms and hypertetraploids occurring in greater than 80% of the histograms. (11 Refs) (In JPN)

9. STUDIES OF DNA SYNTHESIS AND PLOIDY PATTERN OF HEPATOCYTES IN LIVER CIRRHOSIS AND HEPATOMA BY RADIOAUTOGRAPHY AND MICROSPECTROPHOTOMETRY.

Koike Y, Suzuki Y, Nozawa K, Kamijyo K, Yamamura S, Akahane Y, Kiyosawa K, Nagata A, Huruta S, Nagata T
Second Dept. Internal Medicine, Faculty Medicine, Shinshu Univ., Matsumoto-shi, Nagano Pref. 390, Japan
Kanzo; 22(3):413-421 1981

In order to determine the cell kinetics of hepatocytes in liver cirrhosis and hepatoma, both the DNA synthesis, by means of 3H-thymidine (3H-TdR) radioautography, and the DNA content of hepatocytic nuclei, by means of Feulgen-microspectrophotometry, in cirrhosis and the noncancerous portion of hepatoma with cirrhosis were studied. The incorporation of 3H-TdR into hepatocytes in the noncancerous portion of hepatoma as well as cirrhosis which developed into hepatoma 3 yr later increased markedly. The ploidy classes as measured by microspectrophotometry were widely distributed in the noncancerous portion of hepatoma. Moreover, in the normal liver the DNA content of each nucleus a binucleate cell was almost the same, in contrast with that in paired nuclei the noncancerous portion of hepatoma, which was as different as in hepatoma cells. The ploidy pattern of hepatocytes in patients with liver cirrhosis who had developed hepatoma during follow-up periods of several mo to several yr appears to resemble that in the noncancerous portion of hepatoma. (20 Refs) (In JPN)

10. VARIABILITY OF DNA CONTENT IN THE PROGENY OF CLONOGENIC CELLS FROM RAT TRANSPLANTABLE RHABDOMYOSARCOMA.

Kaminskaia EV, Stepan'ian LI, Vakhtin IuB
Lab. Genetics of Cell Populations, Inst. Cytology, Leningrad, USSR
Tsitologiia; 23(7):811-817 1981

The karyotypic heterogeneity of clonogenic tumor cells during selection on affinity to the lung tissue was studied in random-bred albino rats with transplanted sc rhabdomyosarcoma RA-2. Cytophotometric analysis of DNA content showed no changes in the karyotypic structure of clonogenic populations from generation 16 to generation 28 of selection. The modal class in both small and large lung clones corresponded to 2n-3n, and the most polyploid variants contained up to 6n-6.5n. The majority of lung clones originated from hyperdiploid cells, while the sc tumors contained a large number of polyploid cells. Analysis of the mutation rate showed that clonogenic population of RA-2 contained both the clones with high mutability and the clones with low mutability. (21 Refs) (In RUS)

11. ICRF 159-INDUCED CELL-CYCLE PERTURBATION IN VITRO: ITS RELATIONSHIP TO INHIBITION OF COLONY-FORMING ABILITY.

Edgar DH, Creighton AM
Dept. Immunology, ARC Inst. Animal Physiology, Babraham, Cambridge CB2 4AT, Engl and
Br J Cancer; 44(2):236-240 1981

The effects of single doses of ICRF 159 (Razoxane) on the cell-cycle kinetics of lines of BHK 21S cells in vitro were studied by means of flow microfluorometry (FMF). A characteristic accumulation of cells in the 4n DNA region after 6 hr in the presence of ICRF 159 was evident in cells which were sensitive to the cytotoxic effects of the agent, as judged by colony-forming assays. The subsequent accumulation of 8n cells as the major population within 24 hr indicates that this 6 hr effect is associated with the induction of tetraploidy through abnormal mitosis, rather than reflecting a G2 block of potential value in combination therapy. In ICRF 159-resistant sublines, the cell-cycle distributions were similarly affected, but only by doses of the drug high enough to reduce their surviving fraction. Somatic cell hybrids from crosses between sensitive and resistant cells demonstrated intermediate responses to ICRF 159, both in terms of cell-cycle kinetics and impairment of reproductive integrity. These data suggest a relationship between the two manifestations of the cellular action of ICRF 159, and also a possible predictive role for FMF in the assessment of response to this particular agent. (Author abstract) (14 Refs)

CHROMOSOMAL FRAGILITY AND GENETIC FACTORS PREDISPOSING TO HUMAN CANCER

12. OCCURRENCE OF IN VITRO TETRAPLOIDY IN THE HERITABLE COLON CANCER SYNDROMES.

Danes BS
New York Hosp.-Cornell Medical Center, 525 E. 68th St., New York, NY, 10021
Cancer; 48(7):1596-1601 1981

Increased in vitro tetraploidy occurred in skin cultures derived from all affected patients and some family members at risk studied in families with heritable colon cancer syndromes (15 of 16 Gardner syndrome families, three Oldfield syndrome families, and four families with heritable colon cancer syndrome without polyposis coli) but was not present in all (one Gardner syndrome family, 16 of 19 familial polyposis coli families, and two Turcot syndrome families). Seven of 97 controls, family members by marriage, showed increased in vitro tetraploidy. None of these seven had a family history of colonic cancer but four had a family history of other solid tumors. Such in vitro studies illustrated that the occurrence of in vitro tetraploidy should be determined in families rather than individuals in order to determine whether all patients clinically affected show increased in vitro tetraploidy and vertical transmission that can be documented. (Author abstract) (21 Refs)

13. THE SURGICAL MANAGEMENT OF HEREDITARY MULTIFOCAL RENAL CARCINOMA.

Berg S, Jacobs SC, Cohen AJ, Li F, Marchetto D, Brown RS
Dept. Medicine, Harvard Medical Sch. at Beth Isreal Hosp., 1180 beacon St., Brookline, MA, 02146
J Urol; 126(3):313-315 1981

A family was described recently in which renal carcinoma developed in 10 members in three consecutive generations. The cancer tended to develop in patients at an early age, and to occur in both kidneys and at multiple sites more frequently than in nonfamilial renal cancer. The finding of a balanced reciprocal translocation between chromosomes 3 and 8 in affected family members suggests that an inherited genetic defect predisposes to the development of this cancer in middle-aged patients and offers a marker for screening individuals at risk. We herein discuss the surgical management of four family members, the proband and three relatives, who were discovered on screening to have bilateral, multifocal renal cancer. Certain compromises in the principles of radical tumor surgery have proved effective in these four patients. Partial nephrectomy has resulted in total extirpation of the bilateral tumors with survivals of 2 to 4 yr without need for chronic dialysis. The sequential order of surgical procedures is important since partial nephrectomy of the least affected side first allows a total nephrectomy on the more affected side to be done later, when necessary, without transient renal failure. (Author abstract) (10 Refs)

14. FAMILIAL RETINOBLASTOMA AND CHROMOSOME 13 DELETION TRANSMITTED VIA AN INSERTIONAL TRANSLOCATION.

Strong LC, Riccardi VM, Ferrell RE, Sparkes RS
Dept. Medical Genetics, Univ. Texas System Cancer Center, Houston, TX, 77030
Science; 213(4515):1501-1503 1981

Surviving persons from a kindred in which retinoblastoma occurred over four generations, transmitted by eight unaffected individuals, underwent chromosomal analysis. The results revealed that the development of retinoblastoma was associated with a constitutional chromosome deletion del(13)(q13.1q14.5) and that the unaffected transmitting state was associated with a balanced insertional translocation. These findings indicate that predisposition to retinoblastoma may be attributed to the loss of specific genetic material and that a chromosomal mechanism may explain apparent lack of gene penetrance in certain families. The development of unilateral, and not bilateral, retinoblastoma suggests either that the chromosome deletion is different from the mutation of heritable retinoblastoma in general, or that the chromosome deletion lessens the probability of subsequent somatic carcinogenic events. (Author abstract) (19 Refs)

15. LYMPHOCYTE CHROMOSOME SURVEY IN 42 PATIENTS WITH RETINOBLASTOMA: EFFORT TO DETECT 13Q14 DELETION MOSAICISM.

Motegi T
Dept. Pediatrics, Tokyo Univ. Branch Hosp., 3-28-6 Mejirodai, Bunkyo-ku, Tokyo 112, Japan
Hum Genet; 58(2):168-173 1981

An attempt was made to detect a relatively low-proportion mosaicism of 13q14 deletion among 42 retinoblastoma (RB) patients (27 males, 15 females) with an apparently normal phenotype except for RB. Three patients showed abnormal karyotypes: 46,XY,del(13)(q14.1q14.3)/46.XY; 46,XX,del(13)(q14.1q14.3)/46,XX, and 46,XY,del(13)(q14.1q21.2). Neither aneuploidy nor structural aberrations of other than chromosome 13 were found. Thirty-nine patients were diagnosed as having a normal karyotype. including two patients classified as normal. The clinical case reports and cytogenetic studies of the three patients with 13q- cell line in lymphocytes are presented. The data suggested that the frequency of RB cases with a 13q- cell line in lymphocytes may be greater than that which was previously reported. (30 Refs)

16. ENHANCED REACTIVATION OF ULTRAVIOLET-DAMAGED HERPES VIRUS IN ULTRAVIOLET PRETREATED SKIN FIBROBLASTS OF CANCER PRONE DONORS.

Coppey J, Menezes S
Institut Curie, Section de Biologie, 26 rue d'Ulm, 75231 Paris Cedex 05, France
Carcinogenesis; 2(8):787-793 1981

The enhanced reactivation (ER) of UV-damaged nuclear replicating DNA viruses was studied in host cells treated with UV prior to infection. Host cells were from normal (N), xeroderma pigmentosum (XP), excision proficient XP (XP variant), xerodermoid (XD), XP heterozygote (XH), epidermodysplasia verruciformis (EV), and miscellaneous donors. Cells received 260 nanom UV radiation (0.1-25 Joules/square meter [m2]) 0-60 hr before infection with intact (HSV) or UV-irradiated herpes simplex virus (UV-HSV). ER was max for all cell lines when the interval between irradiation of the host cells and infection with virus was 36 hr. In N, XH, XD, XP variant, EV Mibelli's porokeratosis, diffused nevomatosis, and Down's syndrome cell lines, ER was max at a UV dose of 15 Joules/m2. In XD, EV, and XP variant cells the ER was increased 10-fold over the ER in N cells. Max ER was obtained in three groups of XP cells with UV doses of 0.1, 0.3, and 2 Joules/m2. The results demonstrate that UV-HSV undergo ER when host cells are exposed to UV prior to infection. The ER is apparently brought about by an as yet undescribed transitory DNA repair mechanism in the host cells. (54 Refs)

17. CHROMOSOME ABNORMALITIES IN DOWN'S SYNDROME PATIENTS WITH ACUTE LEUKEMIA.

Kaneko Y, Rowley JD, Variakojis D, Chilcote RR, Moohr JW, Patel D
Dept. Medicine, Box 420, Univ. Chicago, 950 East 59th St., Chicago, IL, 60637
Blood; 58(3):459-466 1981

Chromosome and cytologic studies were performed on three Down's syndrome (DS) patients with acute nonlymphocytic leukemia (ANLL). All three patients had an aneuploid clone in their leukemic cells: 50,XX,+6,19,+21,+22, 48,XX,+8,+21, and 47,XY,+8,-21,+dic(21:21)(p13;p11). Every patient appeared to have acute undifferentiated leukemia when the blast cells were examined with Wright-Giemsa stain; cytochemistry studies, however, showed that the leukemic blasts were in an early stage of myeloid differentiation. The two patients with +8 had a preleukemic phase; the blast cells of the patient with an extra number 19 and number 22 could not be differentiated morphologically from those of the two patients with an extra number 8. Our finding and a review of data on 40 other patients suggest that most DS children with ANLL have hyperdiploidy, which is usually related to gains of C, F, and/or G chromosomes, and that the abnormalities of +8 and of +19,+22 in DS children may be associated with acute leukemia (AL) in an early stage of myeloid differentiation. (Author abstract) (41 Refs)

18. LIGHT-INDUCED CHROMATID DAMAGE IN HUMAN SKIN FIBROBLASTS IN CULTURE IN RELATION TO THEIR NEOPLASTIC POTENTIAL.

Parshad R, Gantt R, Sanford KK, Jones GM, Camalier RF
Dept. Pathology, Coll. Medicine, Howard Univ., Washington, DC, 20059
Int J Cancer; 28(3):335-340 1981

Skin fibroblasts from ataxia telangiectasia and xeroderma pigmentosum (XP) donors and from the XP sib (possible heterozygote), all genetically predisposed to a high risk of cancer, show an increased susceptibility to light-induced chromatid breaks after culture in vitro. Light-induced chromatid breaks were shown previously to result from generation of hydrogen peroxide (H2O2) during light exposure. The level of susceptibility attained is significantly higher than that observed in 13 lines of fibroblasts from normal skin of donors ranging in age from 3 days to 92 yr or from fetal skin tested at various population doubling levels. Two lines of normal skin fibroblasts transformed by chemical carcinogens to neoplastic cells also show a significant increase in susceptibility as compared with their untransformed controls. These data indicate for human cells, as reported earlier for mouse cells, an association between enhanced susceptibility to light-induced chromatid damage and neoplastic potential; this association is further supported by the high susceptibility of cells derived from a human adenocarcinoma. Two observations are consistent with the concept that the increased susceptibility does not result from greater initial damage to the DNA of the neoplastic cells. First, activities of the ubiquitous H2O2 scavenging enzyme, glutathione peroxidase, are similar in the paired normal and neoplastic cell populations. Second, cells of the paired lines are equally sensitive to DNA breakage by exogenous H2O2. The enhanced susceptibility associated with neoplastic potential may result from an impaired capacity to repair DNA rather than a greater initial sensitivity of the neoplastic cells to the damaging agent. (Author abstract) (35 Refs)

CHROMOSOMES OF HUMAN CELL LINES AND TUMORS IN VITRO

19. ESTABLISHMENT OF A CELL LINE OF HUMAN SKIN SQUAMOUS CELL CARCINOMA IN VITRO.

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Dept. Dermatology, Yamagata Univ. Sch. Medicine, Yamagata-city, Yamagata, 990-23, Japan
Br J Dermatol; 105(2):125-132 1981

A cell line of a squamous cell carcinoma of human skin (HSC-I) has been established in vitro, and successfully maintained proliferative in continuous tissue culture for about 2 1/2 yr since March 1978. Another cell line (HSC-Ib) has been established in vitro from the recurrence of the same cancer. It has been maintained for about 8 mo since December, 1979. 3T3 feeders were used in the initial cultures in both cases. The cells grow in a monolayer in vitro and are epithelioid with anaplastic features. Chromosome analysis of HSC-I, frozen and thawed HSC-I, the transplanted tumor in a nude mouse and HSC-Ib all showed hypotetraploidy with the modal number 80, which reconfirms that HSC-I derives from the original skin tumor. The cell line is available to other investigators. (Author abstract) (14 Refs)

20. ESTABLISHMENT OF ATTACHED AND NON-ATTACHED CELL LINES FROM AN UNCOMMON HUMAN GLIOMA.

Westermark B, Larsson E, Brunk U, Lubitz W, Mark J
Wallenberg Lab., Univ. Uppsala, Uppsala, Sweden
Int J Cancer; 28(3):341-351 1981

A new cell line, U-706, established from an uncommon human glioma (possibly giant-cell glioblastoma) is reported in this communication. The tumor gave rise to two permanent sublines, one attached (U-706M) and one non-attached (U-706S) cell line. The growth characteristics, chromosome banding pattern, electronmicroscopic picture and cell surface characteristics of the two sublines are described. (Author abstract) (23 Refs)

21. PLURIPOTENT, ERYTHROCYTIC AND GRANULOCYTIC HEMOPOIETIC PRECURSORS IN CHRONIC GRANULOCYTIC LEUKEMIA.

Hara H, Kai S, Fushimi M, Taniwaki S, Ifuku H, Okamoto T, Ohe Y, Fujita S, Noguchi K, Kanamaru A, Nagai K, Inada E
Div. Blood Transfusion, Hyogo Coll. Medicine, 1-1, Mukogawa-cho, Nishinomiya, Hyogo 663, Japan
Exp Hematol; 9(8):871-877 1981

Using methylcellulose culture techniques, we investigated the behavior of committed and pluripotent hemopoietic precursors (CFUMIX) in marrow cells and blood from patients with chronic granulocytic leukemia (CGL) in the chronic phase whose marrow cells showed the presence of Ph1 chromosomes. The relative concentrations of the marrow precursors in CGL were nearly equal to those in control patients. The mean nucleated cell count in marrow fluid from the patients, however, was 6.3x that of control values. As a result, the mean concentrations per unit vol of the hemopoietic precursors in CGL were significantly higher than those in control patients. Furthermore, the presence of erythropoietin (Ep) independent BFUE giving rise to erythropoietic bursts in the medium without the addition of Ep was demonstrable in marrow cells and blood. In the peripheral blood, the increment in numbers of CFUC, CFUE, BFUE, and CFUMIX in accordance with the WBC count was observed. The present results are consistent with the theory that the clonal expansion in CGL occurs at the level of pluripotent hemopoietic precursors and suggest that CFUMIX in CGL can differentiate into CFUE along the erythropoietic pathway and that a regulatory defect in CGL is present in both granulocytic cells and erythrocytic cells. (Author abstract) (26 Refs)

22. HODGKIN'S DISEASE: ESTABLISHMENT AND CHARACTERIZATION OF FOUR IN VITRO CELL LINES.

Diehl V, Kirchner HH, Schaadt M, Fonatsch C, Stein H, Gerdes J, Boie C
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J Cancer Res Clin Oncol; 101(1):111-124 1981

Four in vitro cells established from the pleural effusions of two Hodgkin's disease (HD) patients and from the blood and bone marrow of a third were characterized morphologically, immunologically, and biochemically. The malignant nature of the cultured cells was confirmed by the presence of structural and numerical chromosome abnormalities, the monoclonality of marker chromosomes, and the lack of Epstein-Barr virus-specific antigens. The cells gave rise to tumors in nude mice following intracranial transplantation and induced sc tumors when embedded on plasma dots before transplantation. All four lines were positive for Ia-like antigens, T-cell receptors, acid phosphatase, and acid esterase; they were negative for lysozyme peroxidase, chloracetate esterase, surface Ig or cytoplasmic Ig (CIg), and receptors for complement 3b, complement 3d, IgG-FC, and mouse or sheep RBC. Except for the lack of CIg in the in vitro cells, the marker pattern corresponded to that of Hodgkin's and Sternberg-Reed cells in biopsy material. The phenotype was not that of B cells, T cells, myeloid cells, monocytes, or macrophages. (26 Refs)

23. HUMAN CELL TRANSFORMATION BY SIMIAN VIRUS 40. BIOLOGIC FEATURES OF CLONED LINES.

Sack GH, Obie C
Dept. Medicine, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Exp Cell Res; 134(2):425-432 1981

Nine lines of doubly cloned Simian Virus 40 transformed human fibroblasts have been isolated. Precrisis in vitro characteristics of growth rate, saturation density, T antigen expression, growth in methylcellulose suspension, protease production and infectious center formation were widely divergent, although distinct for individual lines. Lines with higher T antigen expression had higher growth rates and saturation densities but grew less well in methylcellulose. Chromosome counts in most proliferating lines were in the 38-48 range; one line had 67, whereas another, poorly growing line showed 22. No distinguishing chromosomal abnormalities were present. This biologic heterogeneity suggests distinct molecular differences underlying transformation in the lines and emphasizes the importance of considering various factors as indicative of the transformed state. (Author abstract) (33 Refs)

24. INDUCTION OF TUMOR RESISTANCE IN MICE BY HYBRID CELL LINES BETWEEN HUMAN ACUTE L EUKEMIA AND MOUSE MYELOMA CELLS.

Kawashima K, Watanabe E, Isobe K, Suzuki H, Kato Y, Minami S, Nagura E, Ogura M, Yokomaku S, Yamada K, Nagai Y, Takahashi T
First Dept. Internal Medicine, Nagoya Univ., Sch. Medicine, Showa-ku, Nagoya 466, Japan
Igaku No Ayumi; 116(9):770-772 1981

Three hybrid cell lines were obtained from human acute lymphatic leukemia (ALL) and BALB/c mouse myeloma cells (NS-1). They were morphologically all lymphocytic. Absorption tests revealed that they lacked human leukocyte antigen (HLA)-A9 which was expressed in the human ALL cells. Chromosomal analysis showed clone 5 to be diploid, and clones 6 and 12 to be tetraploid, with 1-9 of the D, E, F, and G group human chromosomes. When 5 x 10(6) clone-5,-6, and-12 cells were injected into BALB/c nu/nu mice sc, all the mice developed tumors (at least 0.5 x 0.5 cm) within 2 wk just as did those injected with the NS-1 tumor, and they later died. However, when 1 x 10(7) cells of clones 5, 6, and 12 were injected into BALB/c mice sc, tumors developed in 5/10, 8/10 and 9/10 mice, respectively and, although the tumors were as large as 1.5 cm in some of the mice, the tumors regressed naturally within 1 mo in all of the mice. All of the control mice that were injected with NS-1 tumors developed tumors and 9/10 died within 2 mo. When the BALB/c mice that had been injected sc with 5-10 x 10(6) hybrid cells and had rejected them were challenged by 5 x 10(6) NS-1 tumor cells sc, although tumors were produced in some of the mice in each group almost all the tumors regressed naturally, and tumor deaths occurred in only 2/10, 0/5 and 0/10 of the mice immunized with clones 6, 5 and 12, respectively. When 5 x 10(6) BALB/c-derived Meth-A tumor cells were injected into the mice that were resistant to NS-1 tumors, all of the mice died as did the control mice, the resistance being immunospecific. (10 Refs) (In JPN)

CHROMOSOMES OF ANIMAL CELL LINES AND TUMORS

25. ORIGIN OF MOUSE EMBRYONAL CARCINOMA CELLS AND THE POSSIBILITY OF THEIR DIRECT ISOLATION INTO TISSUE CULTURE.

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Dept. Genetics, Univ. Cambridge, Downing Street, Cambridge CB2 3EH, England
J Reprod Fertil; 62(2):625-631 1981

Various types of investigation using cultured embryonal carcinoma (EC) cells from mice are outlined. The relationship of such cells to cell lineages in normal embryos is discussed. EC cells are characterized by pluripotency. Phenotypically they are similar to primordial germ cells. Cell lines vary in their growth characteristics in vitro and in their capacity to differentiate. They are usually aneuploid, but nearer to normal chromosome number than other mouse tumor cell lines. EC cells have the experimental advantages of accessibility, scale, and ease of manipulation and modification, and are suitable for biochemical and immunological studies. Any stage of embryo between 2-cell and 7.5 days may give rise to teratocarcinoma. After 7.5 days only teratomas occur. Since stem cells of teratocarcinomas are pluripotential, they arise from germ cells or pluripotential embryonal cells. In vitro results may be affected by cellular environmental factors and by selective factors inherent in culture methods. Pluripotential embryonic cells may be obtainable directly from embryos. The 3.5 day blastocyst and 6.5 day egg-cylinder seem to be the most likely sources of such cells. More research under conditions not conducive to cellular differentiation will be required. (39 Refs)

26. AN IMPROVED BASAL MEDIUM FOR Y-1 MOUSE ADRENAL CORTEX TUMOR CELLS IN CULTURE. 2. STABILITY OF STEROIDOGENIC PATHWAY AND CHROMOSOME NUMBER.

Cuprak LJ, Berman HM
Medical Res. Service, Veterans Admin. Medical and Regional Office Center, Togus, ME, 04330
In Vitro; 17(7):570-576 1981

Y-1 cells were passaged weekly for 6 wk in MACT IV medium without a period of adaptation to this basal medium that requires 1% dialyzed fetal bovine serum as a supplement. The steroid pathway and chromosome number, reported earlier for this cell line under culture conditions that used much higher concentrations of nondialyzed sera, remained stable despite dialysis and reduction of the fetal bovine serum to 1%. (Author abstract) (13 Refs)

27. HYBRIDIZATION OF A MOUSE T-CELL LYMPHOCYTE LINE (HB1) WITH A POLYOMA VIRUS-TRANSFORMED MOUSE FIBROBLAST LINE.

Berebbi M, Foa C, Barra Y, Simonetti J, Meyer G
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Exp Cell Res; 134(2):445-456 1981

The establishment of permanent T-lymphocyte cell lines by transformation with DNA viruses has not yet been achieved. This paper reports the successful transfer of polyoma virus genome into T-lymphocyte cells by somatic hybridization. A T-lymphocyte clone, HB1, derived from (DBA/2J x AKR) spleen cells, isolated in vitro by cloning in semi-solid agar, was fused with a polyoma (Py) virus-transformed fibroblast (C3HPy, clone 1). The authenticity of the hybrid C3H/HB was established by chromosome and histocompatibility antigen studies. This initial population and the various clones retained T-lymphocyte characteristics such as morphological appearance, growth properties (suspension culture) and differentiation antigen (Thy 1-2). The hybrid cell line and the various clones presented all the characteristics of Py transformation. Namely, they carried the Py genome originating from the fibroblastic parent and maintained Py virus tumor-associated antigens (TSTA, TSSA and T antigens). In most respects, this hybrid population resembled the C3HPy/Cl1 parent and exhibited the same tumorigenicity. (Author abstract) (28 Refs)

28. ULTRASTRUCTURAL, CELL MEMBRANE, AND CYTOGENETIC CHARACTERISTICS OF B-CELL LEUKEMIA, A MURINE MODEL OF CHRONIC LYMPHOCYTIC LEUKEMIA.

Slavin S, Weiss L, Morecki S, Bassat HB, Leizerowitz R, Gamliel H, Korkesh A, Voss R, Polliack A

Dept. Medicine, Immunology Res. Lab., Jerusalem, Israel

Cancer Res; 41(10):4162-4166 1981

A murine model of a spontaneous, transplantable BALB/c B-cell leukemia (BCL1) is described. Extreme leukemia and splenomegaly develop in H-2d-compatible recipients of tumor cells. Tumor cells are medium to large lymphocytes that can be transformed in plasmacytoid cells following in vitro stimulation with lipopolysaccharide. Karyotype analysis of transformed tumor cells reveals 36 chromosomes with several monosomies and 7 marker chromosomes. The ultrastructure of the tumor cells was studied using transmission and scanning electron microscopy. Although the appearance of tumor cells seems normal by morphological criteria, an impaired capping ability was documented using the fluorescein-conjugated concanavalin A-binding test. Impaired capping ability was documented before leukemia was overt as early as 1 to 3 days following inoculation of tumor cells. The B-cell leukemia (BCL1) provides a useful murine model for the study of various aspects of human bone marrow-derived malignant disorders. (Author abstract) (28 Refs)

29. IMMUNOPATHOLOGY OF NATURAL AND EXPERIMENTAL LYMPHOMAS INDUCED BY WILD MOUSE LEUKEMIA VIRUS.

Bryant ML, Scott JL, Pal BK, Estes JD, Gardner MB

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Am J Pathol; 104(3):272-282 1981

Naturally occurring lymphomas of Lake Casitas (LC) wild mice, and the lymphomas induced by LC murine leukemia virus (MuLV) in Swiss mice from the National Institutes of Health, displayed remarkably similar gross, microscopic, and functional characteristics. They spared the thymus, arose primarily in the splenic red pulp, became leukemic, and were comprised of stem cells lacking classic T- and B-cell markers. Cytoplasmic and surface Ig were undetectable in 34 of 35 spontaneous LC lymphomas and in any of 10 LC MuLV-induced lymphomas in NIH Swiss mice. Assays for Ig secretion, complement (C'3) and Fc receptors, Thy 1.1,2 antigens, Ly 1,2 antigens, and erythroid and myeloid markers were negative on all of the spontaneous and experimental lymphomas. Cell lines were derived from five spontaneous lymphomas of LC mice. Three lines were characterized as null cells, one line as B cells, and one line as macrophages. All cell lines were diploid. The wild mouse spontaneous lymphomas, and lymphomas experimentally induced by LC MuLV in laboratory mice, provide a useful model for childhood acute lymphoblastic leukemia and for study of the early steps of B-lymphocyte differentiation. (Author abstract) (64 Refs)

GENE MAPPING STUDIES

30. CHARACTERIZATION OF THE PHILADELPHIA CHROMOSOME BY GENE MAPPING.

Geurts van Kessel AH, Ten Brinke H, Boere WA, Den Boer WC, De Groot PG, Hagemeijer A, Meera Khan P, Pearson PL

Dept. Cell Biology and Genetics, Erasmus Univ., Rotterdam, Amsterdam

Cytogenet Cell Genet; 30(2):83-91 1981

Chinese hamster x human and mouse x human somatic cell hybrid lines were obtained using circulating WBC from six chronic myeloid leukemia patients. All six patients carried the Ph1 translocation, t(9q+;22q-), characteristic of chronic myeloid leukemia, in their dividing immature granulocytes. Analysis of independent hybrid clones yielded the following results: 1. The chromosome 9 markers, soluble aconitase and adenylate kinase-1, segregated with the 9q+ derivative. The latter marker has previously been localized to 9q34. 2. The chromosome 22 markers, mitochondrial aconitase, N-acetyl-alpha-D-galactosaminidase, and arylsulfatase-A, also segregated with the 9q+ derivative. Mitochondrial aconitase has recently been assigned to 22q11--22q13. No evidence was obtained either for reciprocity of the translocation or for variations in breakpoints in different patients. The results reported in this paper provisionally assign the gene for mitochondrial aconitase to a region distal to the breakpoint in 22q11. (Author abstract) (25 Refs)

31. CHARACTERIZATION OF A COMPLEX PHILADELPHIA TRANSLOCATION (1P-;9Q+;22Q-) BY GENE MAPPING.

Geurts van Kessel AH, Van Agthoven AJ, De Groot PG, Hagemeijer A

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Hum Genet; 58(2):162-165 1981

The results of an investigation in which gene mapping methods were applied to a complex Philadelphia chromosome (Ph1) translocation (1p-;9q+; 22q-) are described. A karyogram of a bone marrow cell of a patient with chronic myeloid leukemia (CML) is presented which shows the complex Ph1 translocation (1p-;9q+;22q-). The breakpoints in chromosome 9 and 22 appeared to be similar to those usually found in Ph1-positive CML, namely in bands q34 and q11, respectively. The breakpoint in chromosome 1 was in band p32. Primary and secondary hybrid cell lines were obtained after fusion of peripheral WBC from this patient with a3 Chinese hamster cells (11 clones) or a23 Chinese hamster cells (10 clones). Detailed chromosome and enzyme data concerning only chromosomes 1, 9, 22, and the derivatives 1p, 9q+, and 22q- are presented in tabular form. A summary of the informative clones in which the presence or absence of enzyme markers are evaluated in the absence of the normal chromosomes which carry these markers is presented. No conclusions could be drawn about translocation of chromosome 9 material or about a possible difference in breakpoint in chromosome 22 when compared to six previously studied related cases. (16 Refs)

32. GENE EXPRESSION IN MURINE HYBRIDS EXHIBITING DIFFERENT MORPHOLOGIES AND TUMORIGENIC PROPERTIES.

Bravo R, Fey SJ, Celis JE
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Carcinogenesis; 2(8):769-782 1981

Highly tumorigenic mouse CLID cells, low-tumorigenic Chinese hamster ovary (CHO) cells, and seven somatic hybrids containing segregated CHO chromosomes were labeled with [35S]methionine. The proteins were extracted and separated by two-dimensional gel electrophoresis followed by one-dimensional electrophoresis. Over 600 polypeptides were assessed. The hybrids all showed similar protein content to the CLID parent. With one exception they also showed some CHO-specific proteins, although at lower levels than in the parent CHO cells. No direct correlation could be made between the occurrence of specific proteins or combinations of proteins and the morphology or tumorigenicity of the cells. Assessment of the major cytoskeletal polypeptides alpha- and beta-tubulin, vimentin, total actin, and isoelectric focusing proteins (IEF) 12, 24, and 31 indicated no demonstrable relationship to the morphology, actin microfilament pattern or tumorigenicity of the hybrids. Except in the case of the related CLID IEF 24 and CHO IEF7 proteins, cytoskeletal proteins co-migrated and showed similar one-dimensional peptide maps. The use of hybridization for gene mapping of chromosomes is suggested for future research. (34 Refs)

33. DILUTE (D) COAT COLOUR MUTATION OF DBA/2J MICE IS ASSOCIATED WITH THE SITE OF INTEGRATION OF AN ECOTROPIC MULV GENOME.

Jenkins NA, Copeland NG, Taylor BA, Lee BK
Jackson Lab., Bar Harbor, ME, 04609
Nature; 293(5831):370-374 1981

The single endogenous DBA/2J ecotropic provirus segregated concordantly with the dilute (d) coat color mutation on chromosome 9 in 53/53 DBA/2J-derived recombinant inbred mouse strains and all seven inbred and mutant strains tested that carry the d allele. Analysis of DNA from a spontaneous DBA/2J d revertant (d+2J) showed that these mice lack ecotropic-specific MuLV DNA sequences and suggested that the dilute mutation resulted from integration of an ecotropic provirus into the mouse genome. (Author abstract) (24 Refs)

34. CHROMOSOME ASSIGNMENT OF THE TUMOR-SPECIFIC ANTIGEN OF A 3-METHYLCHOLANTHRENE-INDUCED MOUSE SARCOMA.

Pravtcheva DD, DeLeo AB, Ruddle FH, Old LJ
Dept. Biology, Yale Univ., New Haven, CT, 06511
J Exp Med; 154(3):964-977 1981

The genetic locus of the serologically defined methylcholanthrene-induced BALB/c sarcoma (Meth A) antigen was mapped through the use of eight somatic cell hybrids between one of the Meth A sarcoma-derived cell lines, Meth A(a), and the Chinese hamster cell line E36 and seven hybrids between the other Meth A-derived line, Meth A(s), and E36. All 15 hybrid expressed Meth A antigen, indicating that in whole cell hybrids, Meth A antigen expression was not detectably affected by the genome of the Chinese hamster parent. In four microcellhybrids (ma 8c, ma 12, mAE 28, and mAE 18) which expressed Meth A antigen, the only mouse chromosome present was an X12 translocation, which they had received from the parental Meth A(a) cells. Hybrid mAE 6, which also expressed the antigen, had chromosome X and 12 in a different arrangement, and in addition, chromosome 1. The Meth A gene was assigned to the distal portion of chromosome 12 (bands F1 and F2). Chromosome 16 may also be implicated. No evidence for linkage between the Meth A coding gene and the H-2 complex was observed. The significance of the close linkage of genes determining Meth A antigen expression with the immunoglobulin heavy chain gene cluster on chromosome 12 and the gamma light chain genes on chromosome 16 is discussed. (48 Refs)

35. ANALYSIS OF THE NONVIRAL ANTIGENS IMMUNOPRECIPITABLE BY SV40 T ANTIBODY FROM SV40-TRANSFORMED HUMAN/MOUSE HYBRID CELL LINES.

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Virology; 114(1):149-160 1981

The expression of nonviral antigens, ie. host-coded proteins with mol wt from 48,000-56,000 (48K-56K) immunoprecipitable from extracts of simian virus 40 (SV40)-infected or -transformed cells by anti-SV40 tumor antibody, was examined in four SV40-transformed human cell lines, one SV40-transformed mouse cell line, and eight SV40-transformed human/mouse somatic cell hybrid cell lines produced by fusion of SV40-transformed human cells with untransformed mouse cells. Differences were found in the patterns of expression of these viral induced proteins among the human cell lines, between the human and the mouse cell lines, and between the human/mouse somatic cell hybrid cell lines and the human lines from which they were derived. Two of the human cell lines expressed only a 55K nonviral antigen; two expressed both a 55K and a 52K nonviral antigen. The mouse cell line expressed both a 55K and a 48K nonviral antigen. Each hybrid cell line expressed a 55K and also a 48K nonviral antigen, except one. The BALB IV-8 hybrid cell line expressed 55K and 52K nonviral antigens. By comparing the tryptic peptides fractionated on cation exchange columns of the nonviral antigens we determined: (1) the 48K nonviral antigen in human/mouse hybrids is encoded by a mouse chromosome. (2) The 52K nonviral antigen in the BALB IV-8 human/mouse hybrid is encoded by a mouse chromosome. It is possibly a precursor to the mouse 48K protein because it contains one extra tryptic peptide in addition to those of the mouse 48K protein, because one peptide has an altered mobility and because the 52K protein is found, so far, only in a human/mouse hybrid that does not exhibit a 48K nonviral antigen. (3) The 55K nonviral antigen in the C57-VII-6 human/mouse hybrid is encoded by a human chromosome. In the BALB I V-8 human/mouse hybrid, there is a 55K protein encoded by a human chromosome and probably a 55K protein encoded by a mouse chromosome. (4) If the gene encoding the human 55K nonviral antigen is located on a single chromosome, it is located on human chromosome 7. (Author abstract) (25 Refs)

MOLECULAR CYTOGENETICS

36. CLASSIFICATION OF CHEMICAL AGENTS AS TO THEIR ABILITY TO INDUCE LONG- OR SHORT-PATCH DNA REPAIR IN HUMAN CELLS.

Francis AA, Snyder RD, Dunn WC, Regan JD
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 83(2):159-169 1981

The excision repair response of normal human fibroblasts (NHF) and of xeroderma pigmentosum (XP) cells to 33 chemicals was compared with that to UV irradiation (which is known to induce 'long-patch' repair of about 90 nucleotides) and to gamma irradiation (which is known to induce 'short-patch' repair of 3-4 nucleotides) by the 5-bromodeoxyuridine (BrdU) photolysis assay that quantitates unscheduled DNA synthesis. The following chemicals induced long-patch repair of 30-70 nucleotides in length and may be classified as UV-mimetic agents: N'-acetoxyacetylaminofluorene, ICR-170, 4-nitroquinoline-1-oxide, diarylcarbamate, 7-bromomethylbenzanthracene, dimethylbenzanthracene-5,6-epoxide, 7beta,8alpha-diol-9beta,10beta-epoxybenzo[a]pyrene, 7beta,8alpha-diol-9alpha,10alpha-epoxybenzo[a]pyrene, ethyl methanesulfonate, methyl methanesulfonate, and N-hydroxy-1-naphthylamine. The other chemicals elicited short-patch repair in NHF cells; the measurable DNA repair activity was at the limit of resolution of the sucrose density gradient technique employed to assay it. XP cells could not repair damage by these latter chemicals to the same extent that NHF cells could. It appears that, for the chemicals tested here, the ability of an agent to elicit a long-patch DNA repair response from NHF is a property of the most active direct-acting carcinogens. (23 Refs)

37. SISTER CHROMATID EXCHANGE, DNA REPAIR, AND SINGLE-GENE MUTATION.

Carrano AV, Thompson LH
Lawrence Livermore Natl. Lab., Livermore, CA
Proceedings of the ICN-UCLA Symposia on Mechanisms in Chemical Carcinogenesis, held in Keystone, CO, February 22, 1981. Available from National Technical Information Service, Springfield, VA, as UCRL-85849:, 22 pp., 1981.

Sister chromatid exchange (SCE) has been studied in cultured mammalian cells with regard to the nature of the inducing lesion, mutation induction, and factors that modify the observed frequency following mutagen exposure. SCEs can be induced by a wide spectrum of DNA lesions and, for nine agents examined, the frequency of induced SCE is linearly related to induced single-gene mutation. Further, a deficiency in DNA repair may alter the expression of both SCE and mutation in a quantitatively similar manner. The frequency of SCE induced by mitomycin-C is suppressed in heterochromatin relative to euchromatin and, in non-dividing lymphocytes, the lesions leading to the formation of SCEs may persist for several mo. (Author abstract)

38. APHIDICOLIN: AN INHIBITOR OF DNA REPAIR IN HUMAN FIBROBLASTS.

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Dept. Genetics, Univ. Coll., Singleton Park, Swansea SA2 8PP, Wales
Carcinogenesis; 2(8):795-797 1981

Normal human fibroblasts and excision-deficient xeroderma pigmentosum (XP) fibroblasts were labeled in vitro with [3H]thymidine. They were then left unirradiated or exposed to 254 nanom UV. Cultures were then reincubated with media containing aphidicolin (2.5 ug/ml), an inhibitor of DNA polymerase alpha; with cytosine arabinoside (araC: 10(-4) M), an inhibitor of semi-conservative and repair replication; with both aphidicolin and araC; or neither compound. Analysis of DNA showed that UV-induced DNA single-strand breaks accumulated equally in normal fibroblasts exposed to araC or to aphidicolin. The presence of both compounds in the medium did not alter the results obtained with only one. Neither compound had any effect on the excision-deficient XP cells. The results indicate that DNA polymerase alpha does play a role in the excision repair of DNA. (14 Refs)

39. ARE INDUCIBLE COMPONENTS INVOLVED IN THE REPAIR OF IRRADIATED NEURONAL AND BRAIN TUMOUR DNA?

Wheeler KT, Wierowski JV, Ritter P
Div. Radiation Oncology, Univ. Rochester Cancer Center, Box 704, 601 Elmwood Ave., Rochester, NY, 14642
Int J Radiat Biol; 40(3):293-296 1981

Repair of irradiated neuronal and brain tumor DNA was studied in male Fisher 344 rats bearing 100-200 mg intracerebral 9L brain tumors irradiated with doses of 12.5 or 25.0 Grays (Gy) of Cesium-137 gamma rays at a dose rate of 9.21 Gy/min. After single doses of either 12.5 or 25.0 Gy, the restoration of chromosomal DNA structure in cerebellar neurons was slower than that in intracerebral tumor cells. DNA repair kinetics after a second dose of 12.5 or 25.0 Gy were identical to those obtained after single dose for both tumor cells and cerebellar neurons. Mean of all values on the plateau region of each curve after a single dose was not statistically different from the mean of values obtained after fractionated doses. Results indicated that the slower DNA repair in permanently nondividing neurons is a fundamental property of these cells and not an artifact of the high dose used initially. Evidence did not suggest that the slower repair results from the need to induce a specific component of the repair system. Consequently, difference in quality, quantity, or type of repair enzymes or difference in accessibility of these enzymes to or interference with their operation at the lesions are more attractive hypotheses to explain the slower DNA repair in neurons as compared with brain tumor cells. (5 Refs)

40. INHIBITION OF SV40 REPLICATION IN SIMIAN CELLS BY SPECIFIC PBR322 DNA SEQUENCES.

Lusky M, Botchan M
Dept. Molecular Biology, Univ. California, Berkeley, CA, 94720
Nature; 293(5827):79-81 1981

Dual-host replicons such as a unit consisting of a bacterial plasmid and genes from a mammalian virus could be of considerable utility in cloning specific genes that are properly the part of the mammalian host's genome and in amplifying the expression of specific cloned eukaryotic genes. Such a dual-host replicon exists: SV40-pBR322, which consists of an Escherichia coli plasmid and the SV40 genome, but it replicates poorly after transfection of simian cells and also shows a reduced ability to retransform E coli following isolation after transfection. Initial experiments showed that this recombinant plasmid did not replicate to any significant extent in transfected CV-1 simian cells and replicated far less well than wild type SV40 in COS7 cells (a permissive strain of CV-1). Two types of experiment showed that these results were not due to a lack of normal A gene expression in the recombinant plasmid but rather were likely due to a cis-acting element present in the chimeric molecule: (1) intact SV40 DNA enzymatically excised from the recombinant could replicate like wild type SV40 in both CV-1 and COS7 cells and (2) when a partial head-to-tail tandem duplication of SV40 was transfected into either CV-1 or COS7 cells, excision of genomic length viral DNA occurred leading to accumulation of detectable form I and form II SV40 DNA. Because SV40 replication in simian cells produces defective viral DNA, plasmid progeny extracted from COS7 cells were used to transform E coli cells; the plasmid DNA was purified from the bacterial hosts and examined for molecules with either a selective transforming ability or a higher replication rate in simian cells: restriction analysis revealed 10 such plasmids that had undergone overlapping deletions near the pBR322 origin of replication, 5 of which replicated in both COS7 and CV-1 cells at rates equal to that of authentic SV40 DNA. This result shows that certain pBR322 sequences interfered with SV40 replication in simian cells. The structures of some of these deletions and their genetic consequences are discussed. The molecular basis for the described restrictions is not known. (18 Refs)

41. CONSISTENT MOLECULAR GENETIC VARIATION IN HUMAN GASTROINTESTINAL CARCINOMAS.

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Nature; 293(5828):146-148 1981

DNA sequences in five human gastrointestinal carcinomas were analyzed by autoradiographic scanning after hybridization to recombinant DNA. The DNA was digested with EcoRI restriction en donuclease, separated by electrophoresis in agarose gel, then blot-transferred and hybridized to P32-labeled DNA probes derived from the 14-or 50-kilobase (kb) regions. Hybridization signals produced by two moderately differentiated sigmoid tumors, a moderately differentiated rectal tumor, an invasive stomach tumor, and a colon tumor are described. Results demonstrated that a consistent genetic variation underlies that apparently random degeneration detected at the chromosome level in advanced human carcinomas. The tendency for hybridization signals to disappear may reflect loss of DNA sequences or their relocation to different sites in the genome. (18 Refs)

42. RELATIONSHIP OF THE RESISTANCE OF MAMMALIAN CELLS TO ACTINOMYCIN D WITH THE CHANGES OF THE KARYOTYPE AND DECREASED PERMEABILITY OF CELL MEMBRANE.

Massino IuS, Kakpakova ES, Kopnin BP, Pogosiants EE

All-Union Cancer Res. Center, Moscow, USSR

Genetika; 17(7):1253-1258 1981

To evaluate the mechanism of resistance to antineoplastic agents, the homogeneously stained regions (HSR) were studied in chromosomes of cultured hamster cells resistant to actinomycin D (AD). Continuous culturing of AD-resistant cells in the absence of selecting agent resulted in gradual disappearance of resistance. Incubation of sensitive and resistant cells with 3H-actinomycin showed marked (approx 50-fold) decrease of label accumulation in resistant cells. These findings indicate that resistance to AD is associated with decreased permeability of cell membrane for AD. The presence of HSR in chromosomes of resistant cells could be interpreted as amplification of genes responsible for the synthesis of certain components of cell membrane. (17 Refs) (In RUS)

43. MOLECULAR PHARMACOLOGY PROGRAM.

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Georgetown Med Bull; 34(4):22-23 1981

Nitrogen mustard and nitrosourea destroy cancer tumor cells by interacting directly with their nuclear macromolecules. For clearer understanding of molecular phenomena, which lead to tumor cell death, different projects are under way. One project tries to define mechanism of nitrosourea toxicity in human and murine bone marrow. Another studies interaction of corticosteroids and alkylating agents and has demonstrated that specific nuclear chromatin targets can be sensitized to nitrosourea by preliminary pretreatment with hydrocortisone. Another project examines potential differences between nuclear chromatin structure and function of normal, tumor, and neoplastic cells, which have developed acquired resistance to nuclear-reactant drugs. The most promising study relates to organization of chromatin and chromosomes on a structure framework known as the nuclear matrix and indicates that drug interaction with this matrix may be extremely deleterious to tumor cells. (no Refs)

EFFECTS OF EXOGENOUS AGENTS ON CHROMOSOMES

44. ON THE QUESTION OF CANCER INDUCTION BY SMALL X-RAY DOSES.

Webster EW

Dept. Radiology, Harvard Medical Sch., Massachusetts General Hosp., Boston, MA, 02114

AJR; 137(4):647-666 1981

There is no proven body of fact that establishes an increase in human cancer after low doses of x or gamma radiation such as those received environmentally, occupationally, or from medical diagnostic procedures; that is, radiation levels below about 10 rad (0.1 Gy). This paper reviews the principal low dose epidemiologic studies that have investigated possible cancer increases. The results of these studies are negative, equivocal, or, when positive, invalidated by methodologic defects or by inconsistency with the feasible carcinogenic effect of background radiation. Despite the lack of direct evidence however, it will never be possible to exclude a very small cancer risk from even the lowest radiation levels, primarily because of statistical limitations in the design of epidemiologic studies. Estimates of cancer risk from low levels of x or gamma ray exposure are therefore based on assumptions regarding the relation between cancer increases and radiation dose. The statistical uncertainties of the meager human data at low doses do not permit unique relations to be established. Nevertheless recent radiobiologic investigations of dose/effect relations for neoplasms in animal populations, for chromosomal damage in human cells, and for malignant transformation in cultured mammalian cell lines suggest that a linear-quadratic relation, when fitted to the human data, provides a reasonable and conservative basis for risk estimation. (Author abstract) (77 Refs)

45. SISTER CHROMATID EXCHANGES IN PERIPHERAL LYMPHOCYTES AFTER PREOPERATIVE MAMMOGRAPHY.

Husum B, Wulf HC, Niebuhr E
Dept. Anesthesia, Gentofte Hosp., DK-2900 Hellerup, Denmark
Radiat Res; 87(3):684-688 1981

The sister chromatid exchange (SCE) rates were studied in the in peripheral lymphocytes of 64 breast cancer patients (17-82 yr old) who had been investigated preoperatively with mammography and in 64 patients (17-82 yr old) without preoperative mammography. The two groups of patients were identical with respect to age, smoking habits, and incidence of malignant breast tumors. Multiple regression analysis of the rate of SCE indicated that preoperative mammography did not influence the SCE rate, nor did patient age or the tumor character. A statistically significant correlation could be demonstrated between SCE and cigarette consumption (r = 0.48, n = 131, P less than 0.001). The results confirm in vitro studies indicating the SCE test system is not useful for evaluation of in vivo exposure to low levels of ionizing radiation. (13 Refs)

46. OXYGEN-EFFECT AS AN INHIBITION OF REPAIR: RADIATION STUDIES ON EXCISION REPAIR DEFICIENT MEI-9L1-EMBRYOS OF DROSOPHILA.

Fritz-Niggli H, Buchi C, Schweizer P
Radiobiologisches Institut, Universitat Zurich, August Forel-Strasse 7, P. O. Box 64, CH-8029 Zurich, Switzerland
Radiat Environ Biophys; 19(4):265-274 1981

A repair deficient mutant of Drosophila melanogaster, mei-9L1, was used to investigate the oxygen effect on excision repair. Embryos were irradiated with 200 kilovolt peak x-rays in air and in oxygen-free N2 20 before and during irradiation. Fundamental differences between mei-9L1 embryos and normal +/+ embryos included the following. The spontaneous lethality of homozygous mei-9L1 embryos was strongly increased coinciding with an increased chromosome instability of the mutants. The 1.75 and 4 hr embryos of the mutants were more sensitive to radiation than normal embryos. The oxygen effect was considerable in the normal embryos, with oxygen enhancement ratios approach 5 in 1.75 hr embryos, while it was practically negligible in 4-hr mei-9L1 embryos and was reduced in 1.75-hr embryos. The nature of the damage depended on the dose, the ability to repair, and on the presence of oxygen. The ability to repair was thus shown to be associated with the oxygen effect. The spontaneous lethality and the increase in radiosensitivity in the heterozygous mei-9L1 embryos depended upon the genotype of the mother. (29 Refs)

47. EFFECT OF X RAYS AND HYPOXIA ON BONE MARROW CELLS OF ALBINO MICE.

Devidze MA
State Univ., Tbilisi, USSR
Soobshch Akad Nauk Gruz SSR; 102(2):425-428 1981

Combined effect of hypoxia and x rays on the yield of chromosome aberrations was studied in random-bred albino mice. Radioprotective effect of hypoxia was recorded after irradiation with 100 and 200 R. Hypoxia failed to reduce the yield of chromosome aberrations in the bone marrow cells after irradiation with 400 R. (5 Refs) (In RUS)

48. RADIOPROTECTIVE EFFICACY OF POLYRIBOINOSINIC ACID-POLYRIBOCYTIDYLIC ACID (POLY I-POLY C). COMMUNICATION I. EFFECT OF POLY I-POLY C ON HEMATOPOIETIC SYSTEM AND SURVIVAL OF IRRADIATED ANIMALS.

Zhukova NA, Palyga GF, Maksimenko AA
Res. Inst. Medical Radiology, Obninsk, USSR
Radiobiologiia; 21(3):358-362 1981

The radioprotective effect of polyriboinosinic acid-polyribocytidylic acid (poly I-poly C) was studied in (CBAxC57Bl)F1 mice. Animals were subjected to a whole body irradiation with 400-950 rads; 2 days prior to irradiation mice received single ip injection of poly I-poly C (2.5 mg/kg). Poly I-poly C increased the survival rate of mice irradiated with 750 rads. The radioprotective effect of poly I-poly C on hematopoiesis (WBC and myelokaryocyte count, the frequency of chromosome aberrations in the bone marrow cells) was recorded only in animals irradiated with 400-650 rads. (18 Refs) (In RUS)

49. FREQUENCY OF CHROMOSOME ABERRATIONS IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES IRRADIATED IN VITRO WITH 60CO GAMMA RAYS AT 1-5 GY AND ANALYZED DURING THE FIRST CELL DIVISION AT DIFFERENT FIXATION TIMES.

Nugis VIu, Piatkin EK
No affiliation given
Genetika; 17(6):1117-1125 1981

The frequency of chromosome aberrations was studied in 50-66-hr cultures of human peripheral blood lymphocytes irradiated in vitro with 60Co gamma rays at 100-500 rads. Sister chromatid staining of the cells in the first division showed that distribution of dicentrics did not depend upon the fixation time. (13 Refs) (In RUS)

50. EFFECT OF LONG-WAVE ULTRAVIOLET RADIATION ON MUTAGENIC AND EMBRYOTOXIC EFFECTS OF CHEMICAL SUBSTANCES.

Prokopenko YIu, Il'in VP, Zhurkov VS
A. N. Sysin Inst. General and Communal Hygiene, Moscow, USSR
Gig Sanit; (7):12-15 1981

The modifying effect of long-wave UV radiation on mutagenic effect of cyclophosphamide (CP) and embryotoxic effect of formaldehyde (FD) was studied in random-bred albino mice and rats. Animals were subjected to 1-mo UV irradiation at 0.5 and 3 erythema-inducing doses followed by intragastric administration of test compounds. CP (3, 9 and 27 mg/kg, 5x) caused a dose-dependent increase of the incidence of aberrant metaphases. UV at below erythema dose did not affect the yield of chromosome aberrations, while UV at 3 erythema-inducing doses increased significantly the frequency of aberrant metaphases. FD administration (0.005, 0.05 and 0.5 mg/kg) to pregnant female rats caused a dose-dependent increase of embryolethality. UV at below erythema dose enhanced resistance to FD, while UV at 3 erythema-inducing doses increased embryolethality. (11 Refs) (In RUS)

51. INDUCTION OF CHROMOSOME ABERRATIONS AND SISTER CHROMATID EXCHANGES BY X RAYS IN DENSITY-INHIBITED CULTURES OF MOUSE 10T1/2 CELLS.

Nagasawa H, Little JB
Lab. Radiobiology, Harvard Univ. Sch. Public Health, Boston, MA, 02115
Radiat Res; 87(3):538-551 1981

The dose-response relationships for the induction of gross chromosomal aberrations and sister chromatid exchanges (SCEs) in density-inhibited cultures of fibroblasts derived from C3H 10T1/2 clone 8 mouse embryo were examined. Changes which occur in cell survival, chromosome aberrations, and SCEs during the repair of potential lethal x-ray damage were also studied. When 10T1/2 cells were irradiated with 200-800 rad in the density-inhibited plateau phase of growth, the cell survival rapidly increased with repair intervals up to 4 hr after x-irradiation; maximal repair occurred after 4-6 hr of delayed subculture. The degree of enhancement of cell survival by potentially lethal damage (PLD) repair was related to the x-ray dose over the range of 200-800 rad. The number of chromosome aberrations decreased progressively when subculture was delayed up to 6 hr after x-irradiation. Thereafter, the aberration frequency remained constant with longer PLD repair periods. There was a mirror image relationship between the increase in cell survival and the reduction in the production of chromosome aberrations. A direct relationship was seen between survival and the prevalence of chromosome aberrations. The change in the induction of SCE during PLD repair showed a more complex pattern. When the cells were subcultured immediately after exposure to 50, 100, and 200 rad of x-rays (no repair), the induction of SCE was increased over baseline (spontaneous) levels in a dose-dependent fashion for doses up to 100 rad with no further increase following 200 rad. When PLD repair was allowed to take place the frequency of SCE induced by 50-200 rad was further enhanced. The dose-response curves for the induction of SCE with PLD repair intervals of 0, 4, and 12 hr after x-irradiation are presented. (26 Refs)

52. ANALYSIS OF STRUCTURAL CHROMOSOME CHANGES AND SCE AFTER OCCUPATIONAL LONG-TERM EXPOSURE TO ELECTRIC AND MAGNETIC FIELDS FROM 380 KV-SYSTEMS.

Bauchinger M, Hauf R, Schmid E, Dresp J
Strahlenbiologisches Institut, GSF, D-8042 Neuherberg-Munchen, W. Germany
Radiat Environ Biophys; 19(4):235-238 1981

Chromosome analyses were performed in peripheral lymphocytes of 32 healthy male workers occupationally exposed for more than 20 yr to 50 Hertz alternating electric and magnetic fields in 380 kilovolt switchyards. All of the subjects were married, and all but one had at least one child. Twelve workers were moderate or heavy smokers, four had stopped smoking within the last 4 yr, and 16 were nonsmokers. The control group was made up of 22 healthy male workers (10 smokers, 12 nonsmokers) of similar age and occupation but without exposure to electromagnetic fields. There were no significant differences in the yield of gaps, acentrics, or dicentric + ring chromosomes between the switchyard workers and controls. No significant differences could be demonstrated for the sister-chromatid exchange-frequencies in the control group and field-exposed group taking into account a subdivision of smokers and nonsmokers. (13 Refs)

53. SISTER CHROMATID EXCHANGE INDUCED BY ANTI-HERPES DRUGS.

Cassiman JJ, De Clercq E, Jones AS, Walker RT, Van der Berghe H
Div. Human Genetics, Univ. Leuven, B-3000 Leuven, Belgium
Br Med J; 283(6295):817-818 1981

The rate of sister chromatid exchange induced by several anti-herpes agents was measured to assess their potential mutagenicity. The agents 5-iodo-deoxyuridine (IDU), 5-trifluoromethyl-deoxyuridine (TFT), and [E]-5-(2-bromovinyl)-deoxyuridine (BVDU)-were incubated at various concentrations with human lymphocytes and fibroblasts, and the rate of sister chromatid exchanges was measured. In lymphocytes and fibroblasts BVDU and IDU did not induce exchange except at concentrations of 50 mg/l, while TFT increased the rate of exchange at a concentration of 0.5 mg/l. The rate of sister chromatid exchange is a sensitive index of chromosomal damage, and these findings provide information on the safety of some of the anti-herpes agents tested. TFT increased the rate of exchange at a concentration that coincides with its minimal anti-viral concentration, but BVDU did not induce exchange at therapeutic concentrations. (Author abstract) (5 Refs)

54. EFFECT OF SUPEROXIDE DISMUTASE ON THE CHROMOSOMAL INSTABILITY OF NEW ZEALAND BLACK MICE.

Emerit I, Levy A, Michelson AM
Laboratoire de Cytogenetique, Institut Biomedical des Cordeliers, Paris, France
Cytogenet Cell Genet; 30(2):65-69 1981

The high chromosomal instability in New Zealand black mice was greatly reduced (to normal values) in vivo by repeated injections of bovine superoxide dismutase (Cu-SOD) over a period of 3 wk. The decrease in aberrations occurred in all the mice treated, and the SOD appeared to be effective for all types of aberrations, including chromatid gaps, telomeric constructions, chromatid breaks, telomeric extrusions, and fragments. (Author abstract) (26 Refs)

55. INDUCTION OF SISTER CHROMATID EXCHANGES AND CHROMOSOME ABERRATIONS IN CULTURED MAMMALIAN CELLS BY N-NITROSOCIMETIDINE.

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Cancer Lett; 14(1):71-75 1981

The possibility that N-nitrosocimetidine (NC), formed by the nitrosation of cimetidine (used in the treatment of gastric disorders), induces sister chromatid exchanges (SCE) and chromosomal aberrations in cultured Chinese hamster ovary cells (CHO) was investigated. NC caused a concentration-related increase in both SCE and chromosome aberrations in a concentration as low as 1.2 x 10(-7) M. At a concentration of 1.2 x 10(-4) M the number of SCE was too great to allow accurate counting and chromosome aberrations were induced in more than 90% of the metaphases. The chromosome aberrations observed were all of the chromatid type. On a molar basis, NC was approx two-thirds as potent an inducer of SCE as the gastric carcinogen N-methyl-N'-nitro-N-nitrosoguanidine. These findings constitute further evidence that NC possesses carcinogenic activity. (10 Refs)

56. INVESTIGATIONS INTO SISTER CHROMATID EXCHANGE IN PATIENTS UNDER CYTOSTATIC THERAPY.

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Abteilung fur Humangenetik, Kinderklinik, Medizinische Akademie, Leipziger Strasse 44, DDR-3090 Magdeburg, E. Germay
Hum Genet; 58(2):198-203 1981

Sister chromatid exchange (SCE) studies were performed on somatic cells from 20 Psoriasis vulgaris (PV) patients (15 men, 5 female; 25-80 yr old) and 24 bronchial carcinoma (BC) patients. The PV patients had recieved a 2-yr methotrexate (MTX) treatment. Weekly MTX doses applied po or iv ranged from 12.5-25 mg. BC patients received a MTX (40 mg, iv, weekly with 2-wk intervals between wk of administration) or cyclophosphamide (CY) monotherapy, or a combined chemotherapy. The av SCE rate of 48 healthy volunteers was found to be 9.54 +-2.82 (standard deviation)/cell. The SCE frequency was not found to be dependent on sex or age. The av SCE rate determined for the 24 BC patients prior to cytostatic therapy did not significantly differ from that of healthy controls. In the lymphocyte chromosomes of MTX-treated PV patients a slight increase in SCE was observed 1-2 days after drug application. The SCE values rose from 9.62 +-2.92 (control) to 11.38 +-3.47. No significant difference was seen after 6-7 days without therapy. In the MTX-treated group of BC patients, minor increases in the exchange rate between sister chromatids compared to their SCE control values prior to initiation of therapy despite the high MTX doses of 80, 120, 140, and 160 mg. All patients studied reached their original SCE values after 14 days without therapy. A significant increase in the SCE frequency was observed in BC patients 1 day after CY treatment. The SCE frequency in patients undergoing combined chemotherapy is discussed. (25 Refs)

57. RELATIONSHIP BETWEEN THE YIELD OF SISTER CHROMATID EXCHANGES AND THE DURATION OF TREATMENT OF HUMAN CELLS WITH ETHYLENIMINE DERIVATIVES.

Listopad GG, Chebotarev AN
Lab. Mutagenesis, Inst. Medical Genetics, Moscow, USSR
Biull Eksp Biol Med; 91(7):70-72 1981

Treatment of human peripheral blood lymphocytes with ethylenimine derivatives (thiophosphamide and dipine) produced a dose-dependent increase of the frequency of sister chromatid exchanges (SCE). The yield of SCE also depended upon the duration of exposure. (7 Refs) (In RUS)

58. ONCOGENIC TRANSFORMATION AND CELL LYSIS IN C3H/10T1/2 CELLS AND INCREASED SISTER CHROMATID EXCHANGE IN HUMAN LYMPHOCYTES BY NICKEL SUBSULFIDE.

Saxholm HJ, Reith A, Brogger A
Inst. Pathology, Univ. Oslo, Rikshosptalet, National Hosp., Oslo, Norway
Cancer Res; 41(10):4136-4139 1981

We have scored frequency of transformation and appearance of the oncogenic marker 'long microvilli' in mouse embryo fibroblast C3H/10T1/2 cells in culture for the compound Ni3S2. Furthermore, we have scored for Ni3S2-induced sister chromatid exchange in cultured human lymphocytes. Nickel subsulfide in moderate doses caused morphological transformation to Type I, II, and III foci and induced long microvilli on the cells in the transformed cultures, demonstrating oncogenic transforming ability. Higher doses led to cell lysis after a lag period. The carcinogenic potency of Ni3S2 in this system was not as strong as that of methylcholanthrene. Ni3S2 increased the sister chromatid exchange frequency in human lymphocytes in a marginal, not dose-dependent way. The increased sister chromatid exchange may indicate that the carcinogenic effect of Ni3S2 is genetic rather than epigenetic. (Author abstract) (39 Refs)

59. FAILURE TO INDUCE SISTER CHROMATID EXCHANGES (SCE) WITH METRONIDAZOLE.

Mahood JS, Willson RL
Biochemistry Dept., Brunel Univ., Uxbridge, Middlesex, England
Toxicol Lett; 8(6):359-361 1981

When cultured CHO-K1 and BHK-21 cells were treated with metronidazole for 24 hr and then examined by colchicine block for mitotic figures showing sister chromatid exchanges, no significant differences (p greater than 0.05) were seen between drug-treated and control cultures in an analysis of variance. These results agree with other published reports that metronidazole does not induce micronuclei in vivo in Trichomonas vaginalis, the induction of dominant lethal genes, or unscheduled DNA synthesis in cultured human fibroblasts. (18 Refs)

60. CYTOTOXIC AND CLASTOGENIC EFFECTS OF SOLUBLE AND INSOLUBLE COMPOUNDS CONTAINING HEXAVALENT AND TRIVALENT CHROMIUM.

Levis AG, Majone F
Inst. Animal Biology, Univ. Padua, Padua, Italy
Br J Cancer; 44(2):219-235 1981

Cr(III) and Cr(VI) compounds of varying solubilities have been tested in vitro for their ability to inhibit cell growth and nucleic acid and protein syntheses in BHK cells, to induce alterations in the mitotic cycle in HEp cells, and to increase the frequency of chromosomal aberrations and sister chromatid exchanges (SCE) in CHO cells. All Cr(VI) compounds, and particularly those containing soluble Cr(VI), such as potassium dichromate and zinc yellow, differentially inhibit macromolecular syntheses in BHK cells, that of DNA being always the most affected. Among Cr(III) compounds, which generally have very low cytotoxicity, chromite is particularly active, and inhibits cell growth and DNA synthesis even more than the poorly soluble Cr(VI) compounds. Preincubation in growth medium, with or without metabolizing cell cultures, solubilizes considerable amounts of Cr(VI) from zinc yellow and chromite, but significant amounts are also obtained from the most insoluble Cr(VI) pigments. When BHK cells are treated with such preincubated solns, reduction of soluble Cr(VI) to Cr(III) by cell metabolites is seen with all Cr(VI) compounds, accompanied by decreased cytotoxicity. The same differences between Cr(VI) and Cr(III) compounds apply to the cytotoxic effects on mitosis of HEp cells and the clastogenic effects on CHO cells. The activity of chromite, the only Cr(III) pigment capable of significantly increasing the frequency of SCE, is due to contamination with soluble Cr(VI). In contrast to the very low cytotoxicity of Cr(III), much higher chromium levels are detected in the cells incubated with soluble Cr(III) than with the same concentrations of soluble Cr(VI). 50% and 75% of chromium accumulated in the cells during treatments with Cr(VI) and Cr(III) respectively remains firmly bound to the cells, even when they are incubated for up to 48 hr in normal growth medium. Chromium accumulated in the cells after treatment with Cr(III) is most probably bound to the cell membrane, whereas some of the Cr(VI) is transported through the cell membrane and reduced in the cell nucleus. The results of the present investigation are in agreement with those obtained with the same Cr(VI) and Cr(III) compounds in mutagenicity assays in bacteria and carcinogenicity tests in rodents. A re-evaluation of the mechanisms of chromium carcinogenesis is proposed. (Author abstract) (54 Refs)

61. TUMOUR PROMOTOR PHORBOL-12-MYRISTATE-13-ACETATE INDUCES CHROMOSOMAL DAMAGE VIA INDIRECT ACTION.

Emerit I, Cerutti PA
Lab. Experimental Cytogenetics, Institut Biomedical des Cordeliers, Universite Pierre et Marie Curie, 15, Rue de l'Ecole de Medecine, Paris VI, France
Nature; 293(5828):144-146 1981

The clastogenicity of the strong skin tumor promoter phorbol-12-myristate-13-acetate (PMA), the weak promoter 4-O-methyl-phorbol-12-myristate-13-acetate and the nonpromoter phorbol (P) was compared in phytohemagglutinin-stimulated human lymphocytes. PMA (10 nanog/ml) induced many chromosome aberrations; 4-O-methyl-PMA induced a significant increase in aberrations only at the highest dose (1,000 nanog/ml); and P was completely inactive. The aberration frequencies increased with an increase in PMA exposure from 4 to 72 hr. PMA also induced polyploidization in 72-hr cultures, but it was a weak inducer of sister chromatid exchanges. Superoxide dismutase inhibited the induction of chromosome aberrations, indicating that superoxide radicals were intermediates in aberration formation. (28 Refs)

62. EFFECT OF CYTOMEGALOVIRUS ON ADULT HUMAN CHROMOSOMES.

Sakizli M, Luleci G, Gunalp A
Dept. Molecular Biology, Univ. Hacettepe, Ankara, Turkey
Acta Virol (Praha); 25(4):248-250 1981

The effects of cytomegalovirus infection on adult human chromosomes was studied in skin cell cultures. Chromosome Number 2 seemed to be affected specifically; chromosome abnormality distribution was independent of chromosome length. (Author abstract) (3 Refs)

GENERAL REVIEWS

63. CHROMOSOME ABNORMALITIES, TUMOURS AND DEVELOPMENTAL DISORDERS.

GroppA
Institut Pathologie Med Hochschule Lubeck, Ratzeburger Allee 160, D-2400 Lubeck, W. Germany
Klin Wochenschr; 59(17):965-975 1981

Clonal chromosome disorders occurring or acquired at any postnatal age are often closely related to the origin of tumors. In man the Ph1-chromosome (9; 22) anomaly in CML or the 8; 14 translocation in the African malignant Burkitt Non-Hodgkin lymphoma are, among other cases, prominent examples. On the other hand, constitutive, inherited or novel chromosome anomalies conveyed from the zygote to all tissues of the organism may cause a higher risk for the origin of tumors. Rarely, inheritable minor structural chromosome mutations are known to determine the occurrence of dysontogenic tumors, as eg, nephroblastoma, but it is assumed that more such cases will become elucidated in the future. As a special phenomenon, true hydatiform mole is a tumor of the placental tissue due to a disorder of intragenome regulation. Constitutive or numerical structural chromosome anomalies of man are a frequent cause of early or late abortion or of abnormal development and malformation. Despite the predominating principle of selective fetal elimination, a few anomalies such as Down's syndrome, may escape to longer survival due to the relatively mild effects of chromosome 21 triplication. Trisomies which represent in man the most frequent type of chromosome disorders, can be induced, and systematically studied in an experimental model of the mouse. This allows the elaboration of the developmental profiles of all trisomies (and monosomies) of the mouse. Also, the above mentioned principle of selective elimination of abnormal implants can be analyzed experimentally. Although the developmental span of a trisomic zygote is limited, there is evidence that cells and tissues isolated from the chromosomally abnormal organism can survive much longer. Thus, hemopoietic stem cells, at least in Ts 12 and 19 of the mouse, can be rescued from trisomic fetuses by transferring them to lethally irradiated adult mice, whose blood forming organs may eventually become permanently repopulated by the trisomic cell lineage. This type of experiments is suited for closer analyses of potential function vs defects of chromosomally abnormal cellular systems, eg, with regard to growth and development. (Author abstract) (55 Refs) (In GER)

64. NATURAL HISTORY OF CERVICAL DYSPLASIA.

Spriggs AI
Lab. Clinical Cytology, The Churchill Hosp., Headington, Oxford OX3 7LJ, England
Clin Obstet Gynaecol; 8(1):65-79 1981

Incidence, pathogenesis, etiology, and treatment of cervical dysplasia are reviewed. Occurrence of dysplasia in previously unscreened women ranged from 0.5% to 6.5% (in different studies). The highest incidence of dysplasia was recorded in a 20-29 yr age group, while carcinoma in situ was predominant in a 30-39 yr age group. Follow-up studies of the patients with cervical dysplasia showed progression to invasion in 0.8-21% of the patients. Etiology of cervical dysplasia may be associated with Herpes simplex virus or with condyloma virus. Cytogenetic studies showed the hyperploidy and variation in DNA content. Evidence of aneuploidy was found even in the mild dysplasias. Conservative management of dysplasia (colposcopy followed by local destruction) is currently the treatment of choice. (66 Refs)

65. PRENEOPLASTIC LESIONS OF THE MAMMARY GLAND. (ONCOLOGY OVERVIEW)

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Preneoplastic Lesions of the Mammary Gland (Oncology Overview) Medina, D, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923002; OB-81/02:134pp. 1981

Oncology Overviews are a service of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute. They are retrospective bibliographies containing 100-500 selected abstracts of published research on topics of high interest to cancer investigators. The scope of this Oncology Overview emphasizes the basic biological aspects of preneoplastic and pseudoneoplastic lesions of human, rodent, and canine mammary glands in vivo and in vitro. Induction and modulation of mammary preneoplasias by carcinogens, hormones and other agents, as well as hormonal responsiveness, immunologic aspects, cytogenetics, and angiogenesis studies are presented. Also of interest are metabolic, enzymatic, and histochemical evaluations of preneoplastic breast lesions. In studies of mammary preneoplasias in humans, ultrastructural and histopathological characteristics, radiologic evaluation, cytology of aspirations and secretions, and cytomorphometry are included. Risk estimates of malignant potential of these breast lesions are also considered. The Overview excludes studies purely concerned with the treatment and/or management of patients with breast preneoplasias.

66. THE ROLE OF HUMAN GENETIC MONITORING IN THE WORKPLACE.

Dabney BJ
IBM Corporation, P.O. Box 1900, Boulder, CO, 80302
JOM; 23(9):626-631 1981

The history and current state of some newer short-term tests for occupational genetic monitoring are reviewed. These are: cytogenetics, sister chromatid exchange, body fluid analysis, tests utilizing sperm, and detection of somatic cell variants. Occupational studies on benzene, vinyl chloride monomer, and epichlorohydrin are critically discussed from the standpoints of design and interpretation. It is concluded that these tests are not appropriate for risk assessment at the present time. Their clinical relevance, if any, is unknown. Proper validation and standardization have not been done, and design problems have often clouded the results of previous studies. There is a critical need for further research in the area of occupational genetic monitoring. Future applications should include integration with prospective morbidity and mortality studies, standardization of design and statistical methods, and de velopment of new tests with genetically relevant endpoints. (Author abstract) (44 Refs)

67. ETIOLOGY, ROLE AND DETECTION OF CHROMOSOMAL ABERRATIONS IN MAN.

Fabricant JD, Legator MS
Dept. Preventive Medicine, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
JOM; 23(9):617-625 1981

Genetic aberrations play a major role in human disease. They are responsible for a number of birth defects and have been identified as an important cause of much prenatal mortality. Approx one-half of all conceptuses, for example, have been estimated not to survive to term, and some die so early that they are not even detected by the mother. Not all genetic anomalies appear at birth, however, since a number may result postnatally from environmental agents that have caused single cell mutations (which might develop into a human tumor), and yet others may require a second mutational event and appear even later. Thus, the industrial environment poses special hazards, to both female and male workers, because of the risks of induction of cancer, as well as of impairment of reproductive ability. Industrial cytogenetic monitoring, as a form of preventive medicine, is now possible. This review discusses many of the causes and types of genetic damage and the current cytogenetic techniques, as well as their use in industrial monitoring. (Author abstract) (67 Refs)

68. SISTER CHROMATID EXCHANGES: A REPORT OF THE GENE-TOX PROGRAM.

Latt SA, Allen J, Bloom SE, Carrano A, Falke E, Kram D, Schneider E, Schreck R, Tice R, Whitfield B, Wolff S
Harvard Medical Sch., Boston, MA, 02115
Mutat Res; 87(1):17-62 1981

Sister chromatid exchange (SCE) as a test for mutagenic carcinogens is reviewed. Method of testing is described with respect to the genetic basis for SCE, and to cell types and animal strains for in vitro and in vivo studies. Interpretation of data is explained, including presentation (dose-response curves, data transformation, and units of expression), statistical evaluation, and criteria for negative/positive conclusions (negative agents, positive agents, provisionally positive agents). Test performance is reviewed with citations of literature, chemicals or chemical classes that give anomalous results (deoxycytidine, ascorbate, and methotrexate), chemicals or chemical classes for which the test is well suited (alkylating agents, many DNA-binding agents, certain DNA-base analogues, and agents that cause single-strand breaks), and correlation with mammalian carcinogenicity data. A protocol is suggested using in vitro and in vivo SCE analysis, and non-mammalian systems for detecting mutagens using the SCE procedure. Conclusions on the strengths and weaknesses of the assay, its role in a testing program, and recommendations for future research are presented. (169 Refs)

69. SHORT-TERM TEST SYSTEMS FOR POTENTIAL MUTAGENS AND CARCINOGENS: I. MICROBIAL TESTS (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Short-Term Test Systems for Potential Mutagens and Carcinogens: I Microbial Tests (Oncology Overview) Simmon, V F; Peirce, V; eds This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922903:; OK-81/03:124pp. 1981

Oncology Overviews are a service of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute. They are retrospective bibliographies containing 100-500 selected abstracts of published research on topics of high interest to cancer investigators. This Oncology Overview addresses itself to the development and direct application of short-term, rapid tests or assays in prokaryotic and lower eukaryotic microorganisms which screen for the carcinogenicity or mutagenicity of chemicals and other agents. This scope covers the experimental designs and specificities, modifications and improvements in methodologies, and selections of test vehicles for short-term assays. In addition to reviewing the development of standard procedures, this Overview includes the development of reporting standards for mutagen and carcinogen tests. The review or evaluation of test systems is also covered. This Oncology Overview specifically excludes studies in which the use of short-term test systems appears, more or less, to be incidental to investigations of the molecular mechanism of carcinogen metabolism, activation, DNA alteration, or the binding of carcinogens to macromolecules.

70. ALKALINE SUCROSE SEDIMENTATION ANALYSIS AS AN INDICATOR OF REPAIR CAPABILITY OF XERODERMA PIGMENTOSUM FIBROBLASTS FOR 4-NITROQUINOLINE-1-OXIDE DAMAGE.

Walker IG
Dept. Biochemistry, Univ. Western Ontario, London, Ontario N6A 5C1, Canada
Carcinogenesis; 2(8):691-695 1981

Fibroblasts were obtained from xeroderma pigmentosum (XP) strains in complementation groups designated A, B, C, E, and Variant, and from normal strains designated Ro, Gr, Fa, and Bu. Cells from all groups were exposed to 1 uM 4-nitroquinoline-1-oxide (4NQO) for 1 hr. They were either analyzed immediately or reincubated to allow repair of DNA damage. DNA sedimentation was measured in an alkaline sucrose gradient. In the brief lysis, gradients were allowed to stand in the dark for 30 min before centrifuging. In the long lysis, gradients were allowed to stand overnight before centrifuging. The long lysis technique showed repair of DNA in the normal strains and in the XP variant and group E strains. This repair was 50% complete 3 hr after removal of the 4NQO and fully complete after 6 hr. No repair was demonstrated in XP groups A, B, and C. The brief lysis technique showed DNA repair which was completed by 6 hr after removal of 4NQO. The repair was the same for all strains. The long lysis technique demonstrates a type of DNA damage not apparent under brief lysis. The results with the longer technique parallel results from other methods that indicate that cells from groups A, B, and C do not repair this type of damage. When alkaline sucrose gradients are used to measure DNA damage, the use of both the brief and long lysis methods is recommended. (26 Refs)

OTHER RELATED STUDIES

71. EVIDENCE FOR THE DIFFERENCES IN THE MECHANISMS OF KILLING IN DIPLOID YEAST CELLS EXPOSED TO HYPERTHERMIA AND GAMMA RADIATION.

Deorukhakar VV, Rao BS, Anjaria KB, Madhvanath U
Div. Radiological Protection, Bhabha Atomic Res. Centre, Bombay 400 085, India
Indian J Exp Biol; 19(3):220-224 1981

Cross sensitivity to hyperthermia (51 C) and gamma radiation was investigated in wild type (strains X2180 and BZ34) and mutant (rad 9-4, 51-1, and 52) strains of the diploid yeast Saccharomyces cerevisiae. Compared with the wild type strains, the mutants exhibited high sensitivity to gamma radiation while sensitivity to heat was not significantly different. No correlation between radiation and hyperthermic response in diploid yeast strains was found. Strain BZ34 was more sensitive to hyperthermic killing in the most radioresistant phase of the cell cycle, the radioresistant log phase, as compared to the radiosensitive stationary phase. In cells exposed to radiations (10% or 1% level) budding began within 1 hr and reached a max of approx 90% within 4-6 hr. Cells exposed to hyperthermia gradually increased rate of cell budding only after approx 8 hr and reached a max of approx 90% in about 18-20 hr. The significance of these results in elucidating the differences in mechanisms of induction of cell lethality by hyperthermia and radiation is discussed. (28 Refs)

72. COMPARISON OF SENSITIVITY OF RAD MUTANTS OF DIPLOID YEAST TO HEAT AND GAMMA RADIATION: CELLULAR TARGET FOR HEAT INACTIVATION.

Reddy NM, Rao BS, Madhvanath U
Div. Radiological Protection, Bhabdha Atomic Res. Centre, Trombay, Bombay-400 085, India
Int J Radiat Biol; 40(3):235-243 1981

Wild type and radiation-sensitive mutants rad 53, 54 and 55 of the diploid yeast Saccharomyces cerevisiae, in stationary and log phase were exposed to gamma radiation and hyperthermia (51 C) in order to compare their sensitivity to these agents. The wild type diploid strain exposed to gamma rays showed a sigmoidal survival curve both in stationary and log phase cultures. Log phase cells were significantly more resistant than stationary phase cells. When compared to wild type, the gamma radiation response of the mutants indicated that the mutations in these RAD loci render the cells sensitive in stationary phase and very sensitive in log phase. The response of mutants to hyperthermia was similar to that of wild type cells in both the phases. The log phase cells of both wild type and mutants were more sensitive to heat than stationary phase cells. These results suggest that the RAD loci are not involved in the repair of hyperthermic damage. Since it is known that the products of the RAD genes are involved in the repair of DNA damage, the wild type response of these rad mutants to hyperthermia indicates that the DNA may not be the principal target for hyperthermic killing. Furthermore, the enhanced thermal sensitivity of log phase cells, containing higher amounts of active enzymes and sensitive membrane, strongly suggests that proteins and/or membranes could be the primary targets for thermal inactivation. (Author abstract) (29 Refs)

73. MECHANISMS OF MALIGNANT GROWTH.

Grundmann E
Pathologisches Institut, Universitat Munster, Domagkstrasse 17, D-4400 Munster, W. Germany
Klin Wochenschr; 59(17):931-941 1981

Analysis of invasive malignancy focuses on the particularly high growth rate of tumor cells, and on the aggressive mechanisms of histolysis favoring the infiltration of the malignant cells into the surrounding tissue. Specific significance is attributed to a certain enzyme directed against Type IV collagen, and to the auto-locomotion of tumor cells, properties that may also explain the highest selective process of metastasization in at least three consecutive steps: Tumor cells invade a blood or lymph vessel, they are transported along blood or lymphatic pathways, and they eventually infiltrate foreign tissue after penetration and destruction of blood or lymph vessel walls. Among the factors involved in the process of metastasization, special interest is due to blood coagulation and to the coexistence of different tumor cell subpopulations within a primary. These features of malignant growth are based on the loss of functional differentiation as manifested eg in the loss of tissue-specific nuclear chromatin structures. Tumor development is triggered by the so-called primary factors which always affect the DNA, ie, the cell genome. Chemical carcinogens, viruses, and shortwave or ionizing irradiation induce DNA defects which, however, will be reversed and mended by special repair mechanisms in most cases. Thus, the actual development and spread of malignancy is ultimately due to deficient reparation. Co-factors favoring and promoting carcinogenesis may shorten the latency period, among several other specific chemicals and hormones. Based on current knowledge of tumor dormancy a new concept is proposed for the chronological and morphological sequence of carcinogenesis: Following the development of a primary tumor, certain as yet undefined growth factors and especially immunological factors may be responsible for the development of a progressive tumor disease. (Author abstract) (62 Refs) (In GER)

74. EARLY POSTRADIATION CHANGES IN CHROMATIN FROM RAT THYMUS: MG++ LEVEL AND INTENSITY OF DEGRADATION AFTER EXPOSURE TO ENDONUCLEASES.

Chirkova LP, Ermolaeva NV
No affiliation given
Radiobiologiia; 21(3):335-340 1981

The changes in the Mg++ content and the rate of chromatin degradation were studied in random-bred and Wistar rats irradiated with 600 R. Animals were sacrificed 0.5, 1, and 2 hr after irradiation, and chromatin specimens isolated from the thymus were subjected to spectrofluorometry. There was a 65-90% increase in the Mg++ content and a 2-3-fold increase in the rate of endonuclease-induced chromatin degradation at pH of 6.4-6.5. (16 Refs) (In RUS)

75. MANIFESTATION OF CARCINOGENESIS AS A STOCHASTIC PROCESS ON THE BASIS OF AN ALTERED MITOCHONDRIAL GENOME.

Neubert D, Hopfenmuller W, Fuchs G
Institut fur Toxicologie und Embryopharmakologie, Freien Universitat Berlin, Garystrasse 9, D-1000 Berlin 33, W. Germany
Arch Toxicol; 48(2/3):89-125 1981

Computer calculations are used to show the feasibility of a concept which explains the manifestation of a pathological cell function from a latent state by the phenomenon of extrachromosomal inheritance (through the mitochondrial genome) in mammalian cells. A hypothesis is submitted in which this principle is applied to the process of carcinogenesis. According to this concept, the manifestation of a tumor cell - after the initiation stage - entirely depends on stochastic events, ie, random distribution of mitochondria during cell divisions, with an accumulation of the lesion in a few out of many cells. We feel that this concept comprises a better explanation of many characteristics and peculiarities of the phenomenon of carcinogenesis than do attempts which explain tumor formation as a phenomenon caused by mutation in a nuclear genome. A consideration of the principles presented automatically leads to a number of specific consequences with regard to carcinogenesis. Some of these consequences are discussed. They include: 1. the process of malignant transformation should not be irreversible for all the cells of a progeny; 2. the number of mitochondria in a cell type should be inversely correlated to tumor frequency; 3. the latent period should mainly be determined by the cell division rate and the 'extent' of the initiating event; 4. susceptibility to carcinogenesis may be substantially higher if the number of mitochondria per cell line is increasing or decreasing, ie, during the embryonic and fetal periods; 5. heterogeneous types of cells may arise from a single 'initiated' cell, and 6. the process of malignant transformation should not necessarily be confined to one generation of the species. In addition, experimental approaches to support the submitted concept are suggested. (Author abstract) (91 Refs)

76. DIFFERENCE IN GENETIC EXPRESSION BETWEEN NORMAL AND TRANSFORMED WI-38 CELLS.

Nose K, Okamoto H, Namba M
Dept. Biochemistry, Toyama Medical and Pharmaceutical Univ. Sch. Medicine, Sugitani, Toyama, Japan
Cell Struct Funct; 6(2):93-101 1981

In order to study transformation-specific gene expression, total poly(A)+RNA was extracted from normal WI-38 and Co60-irradiation-transformed WI-38 (CT-1) human diploid fibroblasts, complementary DNA (cDNA) against this RNA was prepared, and hybridization studies of these two nucleic acids were performed; also, radiolabeled proteins from the normal and transformed cells were prepared and examined by two-dimensional gel electrophoresis. Poly(A)+RNA sedimenting from 5S to 23S was hybridized to cDNA fractions greater than 150 bases (av size: 300 bases) in two combinations: homologous (both nucleic acids came from the same cell type) and heterologous (the RNA and DNA came from opposite cell types); considerable hybridization occurred in both cases, showing that there is extensive homology between the poly(A)+RNAs of normal and transformed cells. Approx 200 protein spots were examined electrophoretically from both cell types, first by isoelectrofocusing and then by sodium dodecyl sulfate-polyacrylamide gel analysis followed by autoradiography: two proteins were found in the normal cells that were not present in the transformed cells, and two proteins were found in the transformed cells that were not found in the normal cells. These results indicate that transformation of human fibroblasts is accompanied by only limited alteration in genetic expression. (25 Refs)

77. IN VIVO AND IN VITRO ETHYLENE OXIDE EXPOSURE OF HUMAN LYMPHOCYTES ASSESSED BY CHEMICAL STIMULATION OF UNSCHEDULED DNA SYNTHESIS.

Pero RW, Widegren B, Hogstedt B, Mitelman F
Wallenberg Lab., Univ. Lund, Fack 7031, 220 07 Lund 7, Sweden
Mutat Res; 83(2):271-289 1981

Evidence of toxic exposure to ethylene oxide (EO) in factory workers producing disposable medical equipment was sought in 17 exposed women and 11 unexposed female controls from the same plant. EO exposure was 0.5-1.0 ppb for 40 hr/wk in 12 packers and 5-10 ppb for 8 hr/wk in 4 sterilizers and 1 lab technician, using the measurement of N-acetoxy-2-acetylaminofluorene (NA-AAF)-induced unscheduled DNA synthesis (UDS) in lymphocytes as the assay. The results for the controls in this study agreed with previous results for unexposed subjects: age and/or chromosome aberrations increased in a positive linear manner with increases in NA-AAF-induced UDS. However, the results for the EO-exposed packers were completely different for these two parameters: tendencies toward negative linear correlations were observed that were so divergent from controls (even for this small sample size) that these two groups were shown to be borderline significantly different populations. The data for the other group of exposed workers was nearly significantly different from that for the packers, indicating that perhaps the EO exposure in this group was not high enough to cause a significant reduction in NA-AAF-induced UDS. These results were corroborated by in vitro measurements of EO-induced (0.1-30 milliM) UDS in cultured lymphocytes: at greater than 2 milliM EO, UDS was inhibited, and even at the 0.1 milliM dose where UDS was not affected the exposed cells were sensitized to further exposure to NA-AAF, which caused a 40% cytotoxicity compared with 5% in controls. EO is toxic to lymphocytes and nontoxic doses of EO can sensitize cells to the cytotoxic action of other mutagens. (21 Refs)

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MARCH, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

CLINICAL STUDIES OF CHROMOSOMES IN HUMAN CANCER

1. PROBABLE MECHANISM FOR THE LOSS OF BARR BODY IN HUMAN FEMALE TUMOR WITH SPECIAL REFERENCE TO BREAST CANCER.

Ghosh SN, Shah PN
Endocrinology Div., Cancer Res. Inst., Parel, Bombay 400 012, India
Med Hypotheses; 7(8):1099-1104 1981

The relationship between Barr body frequency (BBF) and human female breast tumors is discussed. A decrease in BBF has been observed in colonic neoplasms. This decrease in BBF is possibly related to reactivation of the second X chromosome with concurrent increase in glucose-6-phosphate dehydrogenase activity. Factors that may be involved in the reactivation of a genetically inactive X chromosome are discussed. Studies of post-menopausal women, G-6PD activity in carcinogen-induced rat breast tumors, and estradiol-17beta treatment of HeLa cells indicate an association between BBF frequency and estrogen. Evidence that both X-chromosomes are active in clonal cultures of undifferentiated female mouse teratocarcinoma stem cells derived from spontaneous ovarian tumors has been presented. Other evidence suggesting that activation of a second X-chromosome is not the true mechanism for loss of X-chromatin is presented. Evidence suggesting that low Barr body counts in highly malignant human breast tumor could be related to elaboration of collagenase from tumor cells at the time of invasion is presented. (35 Refs)

2. CANCER OF THE MALE BREAST. A REVIEW OF 17 CASES.

Kuo SJ, Wang CC, Liu TC, Wu SJ, Peng FK, Lee C
Dept. Surgery, Veterans General Hosp., Taipei, Taiwan
J Formosan Med Assoc; 80(5):523-529 1981

Review of hospital records from 1961-1979 uncovered 17 cases of breast cancer in males, all of whom presented with palpable lumps. Histologically 14 were carcinoma (13 adenocarcinoma, 1 epidermoid carcinoma) and 3 sarcoma (fibrosarcoma, leiomyosarcoma and malignant schwannoma). Karyotypic analyses of six patients chosen at random revealed normal chromosome number but all had abnormal marker chromosomes in the B/D Group and ring chromosomes in the F Group. Subsequent cancers were found in lung (1 case) and gastric and urinary bladder (1 case). Radical mastectomy was used in nine patients; in six with axillary metastases, five received postoperative radiotherapy, one chemotherapy. Four of these five died 2-6 yr after therapy, two of other cancers; one patient was lost to follow-up. Of 11 without axillary involvement, 9 are alive 0.5-10 yr after operation; 2 were lost to follow-up. Six patients survived 5 yr or more. (8 Refs)

3. BILATERAL INCIPIENT GERM CELL TUMOURS OF THE TESTIS IN THE INCOMPLETE TESTICULAR FEMINIZATION SYNDROME.

Nogales FF, Toro M, Ortega I, Fulwood HR
Departamento de Anatomia Patologica, Facultad de Medicina, Avda. de Madrid s/n, Granada, Spain
Histopathology; 5(5):511-515 1981

The implications of bilateral incipient germ cell tumors of the testis observed in two patients with incomplete testicular feminization syndrome (TFS) for the management and early diagnosis of germ cell tumors which develope in a high proportion of patients with TFS are considered. In both cases, clinical features were similar and characteristic of the incomplete form of TFS. At the time of orchidectomy, the patients were aged 13 and 16 yr, respectively. Both were phenotypic females with a 46XY karyotype and had enlarged clitoris, scanty pubic and axillary hair, and underdeveloped breasts. Both patients had had bilateral inguinal hernias since birth. Bilateral orchidectomy was performed in each patient. The excised testes measured 1.6-2 cm in their max diameters. Severe germ cell atypia was found bilaterally in both cases, in 20% of all areas studied in Case I and in 5% of those in the second. This consisted of cells with abundant clear cytoplasm in contact with basal lamina and adjoining Sertoli cells. Their nuclei were twice the size of those of non-neoplastic spermatogonia and some were lobulated with irregular clumping of chromatin and prominent nucleoli. Inspection of multiple yellow nodules seen macroscopically in Case II revealed them to be well-circumscribed and composed of narrow, almost solid tubules lined by closely packed Sertoli's cells, devoid of germ cells; they were considered to be Sertoli's cell adenomatous nodules. (19 Refs)

4. EBV-POSITIVE BURKITT'S LYMPHOMA FROM ALGERIA, WITH A THREE-WAY REARRANGEMENT INVOLVING CHROMOSOMES 2, 8 AND 9.

Philip T, Lenoir GM, Fraisse J, Philip I, Bertoglio J, Ladjaj S, Bertrand S, Brunat-Mentigny M
Service de Pediatrie, Centre Leon-Berard, 28, rue Laennec, 69373 Lyon cedex 2, France
Int J Cancer; 28(4):417-420 1981

Burkitt's lymphoma was diagnosed in a male Algerian child presenting with abdominal and jaw tumors. Viral studies revealed that this non-endemic case was associated with the Epstein-Barr virus. Cytogenetic examination of tumor cells showed a complex three-way rearrangement involving chromosomes 2, 8 and 9. Our report indicates that, in Burkitt's lymphoma, not only simple but also complex translocations involving chromosome 8 may arise. This finding in a North African case emphasizes the need for more detailed study of the clinical, virological and cytogenetic features of Burkitt's lymphoma throughout the world. (Author abstract) (36 Refs)

5. DIRECT CYTOGENETIC STUDIES BY NEEDLE ASPIRATION OF BURKITT'S LYMPHOMA IN GHANA, WEST AFRICA.

Biggar RJ, Lee EC, Nkrumah FK, Whang-Peng J
Environmental Epidemiology Branch, Div. Cancer Cause and Prevention, NCI, NIH, US Dept. of Health and Human Services, Bethesda, MD, 20205
JNCI; 67(4):769-776 1981

With the use of a needle aspiration technique for obtaining tumor material, the direct karyotype of Burkitt's lymphoma cells was examined from 14 Ghanaian patients. The 14q+ chromosome (in addition to other chromosomal abnormalities) was present in 8 (57%) of the 14 patients; 6 of these 8 patients had t(8;14) (q24;q32). One of the remaining two patients had a 8 chromosome deleted, whereas the second had two normal-appearing 8 chromosomes. Other numerical and structural abnormalities were frequent. No correlation between type or frequency of abnormality and clinical status or survival was found. Within cells of the same tumor aspirate, the karyotype abnormalities were generally similar. In three patients, karyotypes from two separate tumor sites (abdomen-bone marrow, 2 cases; right maxilla-left mandible, 1 case) showed identical markers. The same marker was seen in specimens from the initial and second relapse abdominal tumors of one patient. The similarity of chromosomal markers from two sites or in serial studies further supports the concept that African Burkitt's lymphoma is a disease of monoclonal origin. (Author abstract) (19 Refs)

6. NORMAL SISTER CHROMATID EXCHANGE AND CELL CYCLE PROGRESSION IN CULTURED LYMPHOCYTES FROM PATIENTS WITH MALIGNANT LYMPHOMA.

Crossen PE, Fitzgerald PH, Colls BM
(c/o Fitzgerald) Cancer Society New Zealand, Cytogenetics Unit, Christchurch Hosp., Christchurch, New Zealand
JNCI; 67(4):821-824 1981

Twenty patients with malignant lymphoma were examined; all but 2 were untreated or had not recently received therapy. Sister chromatid exchange (SCE) and cell progression through to the third mitotic cycle after phytohemagglutinin stimulation did not differ according to lymphoma type or disease stage, and the lymphoma group as a whole did not differ from 20 normal controls. These findings are contrary to other recent studies of SCE in malignant lymphoma. The only patient who had received recent chemotherapy had the highest SCE score and a greatly accelerated cell cycle response. (Author abstract) (24 Refs)

7. CORRELATIONS BETWEEN THE CLINICAL COURSE, CHARACTERISTICS OF BLAST CELLS, AND KARYOTYPE PATTERNS IN CHRONIC MYELOID LEUKEMIA.

Fleischman EW, Prigogina EL, Volkova MA, Frenkel MA, Zakhartchenko NA, Konstantinova LN, Puchkova GP, Balakirev SA
Cytogenetic Lab., Cancer Res. Centre, AMS USSR, Kashirskoye shosse, 6, Moscow 115478, USSR
Hum Genet; 58(3):285-293 1981

Correlations between karyotype and clinical and morphologic manifestations of chronic myeloid leukemia (CML) were studied. A cytogenetic study of 101 CML patients (87 adults; 14 children less than 16 yr old) was performed. The karyotype of 61 patients was analyzed in the terminal (acute) stage. Standard (9;22)(q34;q11), atypical (10;22), and complex translocations of the Philadelphia chromosome (Ph1) were observed in 95/101, 1/101, and 5/101, respectively. Only Ph1 translocations could be found in the leukemic cells of most of the patients in the chronic phase. Cell lines with some additional karyotype abnormalities were discovered in two patients. Additional chromosome abnormalities were discovered in 4/8 patients in the transitional stage. Cell clones with additional chromosome abnormalities were found in 47/61 terminal phase patients. These clones constituted 4-100% of the total number of cells, usually more than 50%. The chromosome changes in the acute phase of CML were nonrandom and usually involved pairs 8, 17, and 19. The terminal phase patients are divided into four groups according to the type of leukemic cell chromosome alteration; significance of these alterations is discussed. (33 Refs)

8. NONRANDOM CHROMOSOME ABNORMALITIES IN ACUTE LEUKEMIA AND DYSMYELOPOIETIC SYNDROMES IN PATIENTS WITH PREVIOUSLY TREATED MALIGNANT DISEASE.

Rowley JD, Golomb HM, Vardiman JW
Dept. Medicine, Univ. Chicago, Box 420, Chicago, IL, 60637
Blood; 58(4):759-767 1981

Cytogenetic studies were performed on 26 patients who developed acute nonlymphocytic leukemia (ANLL) or a dysmyelopoietic syndrome after treatment of a primary malignancy. Fifteen patients had radiotherapy and chemotherapy, seven had only chemotherapy, and four had only radiotherapy. The median times from diagnosis of the initial disease to the development of bone marrow dysfunction for these treatment groups were 50, 46, and 49 mo, respectively. Twenty-five patients had an abnormal karyotype in myeloid cells. Loss of part of all of no 5 and/or no 7 was noted in 23 of 25 patients with aneuploidy. Loss of no 5 was noted only in patients who previously had malignant lymphoma, whereas loss of no 7 was seen in these patients as well as in those who had other malignancies. Abnormalities of both no 5 and no 7 occurred in 53% of the patients treated with combined therapy and in only 27% of patients treated with either modality alone. Although these changes are distinctly different from those noted in lymphomas, they are similar to those seen in 25% of aneuploid patients with ANLL de novo. (Author abstract) (37 Refs)

9. CHROMOSOMAL ABNORMALITIES IN ACUTE LYMPHOBLASTIC LEUKEMIA.

Bloomfield CD, Lindquist LL, Arthur D, McKenna RW, LeBien TW, Peterson BA, Nesbit ME
Univ. Minnesota Hosp., Box 277, Mayo Building, Minneapolis, MN, 55455
Cancer Res; 41(11,part2):4838-4843 1981

Chromosome abnormalities in acute lymphoblastic leukemia (ALL) and their possible clinical significance are briefly reviewed based upon the literature and 60 cases studied at the University of Minnesota. Almost all cases of ALL appear to demonstrate clonal abnormalities; the major abnormal clone is usually hyperdiploid or pseudodiploid. Among cases of non-T, non-B ALL, at least four translocations appear to be present with an increased frequency: t(9;22); t(4;11); t(11;14); and t(1;3). Patients with these translocations appear to have unique clinical and laboratory findings. Although the presence of abnormal clones does not seem to influence remission duration, the nature of the abnormality does. Patients whose leukemias demonstrate predominantly a pseudodiploid abnormal clone or a translocation have significantly shorter first remissions. Most importantly, among patients with non-T, non-B ALL, the presence or absence of translocations may separate poor responders from good responders. (Author abstract) (42 Refs)

10. CYTOGENETIC OBSERVATIONS IN CHRONIC MYELOID LEUKEMIA (CML) CORRELATIONS OF THE CYTOGENETIC FINDINGS WITH MORPHOLOGICAL CYTOCHEMICAL FEATURES OF BLAST CELLS IN VARIOUS TYPES OF BLASTIC PHASE.

Olah E, Kiss A, Jako J, Balogh E, Rak K
Dept. Pediatrics, Second Internal Clinic, Univ. Medical Sch., Debrecen, Hungary
Neoplasma; 28(3):325-332 1981

Forty-nine cases of chronic myeloid leukemia have been investigated using cytogenetic methods. Twenty-six patients were studied in chronic phase, 23 during the transformation of the disease. Out of the second group of patients, nine were myeloid, five myelomonocytic, two promyelocytic, two megakaryoblastic and five lymphoid in their morphological and cytochemical appearance. Some correlation could be observed between the clinical, morphological, cytological and cytogenetic findings of different subgroups of the blastic phase in CML. The results demonstrate the divergent clonal evolution of transformed blast cells, and emphasize the importance of chromosome investigations - in addition to the early diagnosis of metamorphosis - in distinguishing the different subgroups of the terminal stage of CML. (Author abstract) (22 Refs)

11. CHROMOSOMAL ABNORMALITIES IN ACUTE LYMPHOBLASTIC LEUKEMIA: STRUCTURAL AND NUMERICAL CHANGES IN 234 CASES.

Mitelman F
(c/o A. Sandberg), Roswell Park Memorial Inst., Buffalo, NY, 14263
Cancer Genet Cytogenet; 4(2):101-110 1981

Chromosomal abnormalities were found in cultured bone marrow and blood cells from 218/330 untreated patients and 16 treated patients with acute lymphoblastic leukemia. Five children and two adults (2.1% of the patients) had constitutional abnormalities, as opposed to 0.73% of 3,993 recently surveyed newborn infants. Of the 234 abnormal clones, 119 were pseudodiploid, 86 hyperdiploid, and 29 hypodiploid. Structural changes occurred in 204 cases, either alone (103) or combined with numerical changes (101); numerical changes alone accounted for 30 cases. The most common structural change was the presence of the Philadelphia chromosome associated with a translocation to chromosome 9. Chromosomes 1, 4, 6, 8, 11, and 14 also were involved in the structural changes. Lymphocyte marker studies in 182 cases showed that 72% were null cells, 19% T cells, and 9% B cells. Philadelphia chromosome-positive patients and those in the hyperdiploid category were all classified as having null cell leukemia. (8 Refs)

12. CLINICAL SIGNIFICANCE OF CHROMOSOMAL ABNORMALITIES IN ACUTE LYMPHOBLASTIC LEUKEMIA.

Mitelman F
(c/o A. Sandberg), Roswell Park Memorial Inst., Buffalo, NY, 14263
Cancer Genet Cytogenet; 4(2):111-137 1981

Correlations between chromosome classification and clinical and hematologic findings at diagnosis, and the relation between karyotype and response to treatment, were examined in 173 adults and 157 children with acute lymphoblastic leukemia (ALL). All patients with a modal number greater than 46 and/or the Philadelphia chromosome had non-T-, non-B-cell ALL; children and adults with chromosome translocations and high initial WBC counts tended to have B-cell ALL. Patients with a normal karyotype or pseudodiploidy accounted for most of the T-cell ALL cases. The complete response rate to treatment was 91% for children and 65% for adults. ALL patients with a modal number greater than 50 responded best, and children in this group frequently appeared to be cured. Patients without chromosomal abnormalities or a 6q- also did well. In contrast, patients with t(4;11) or t(8;14) ALL responded poorly and had the shortest survival. Of the non-T, non-B ALL patients, those with a modal number less than 46 and the Philadelphia chromosome had the poorest prognosis and those with a modal number greater than 50, pseudodiploidy, or no abnormalities had the best prognosis. Karyotype was a prognostic variable independent of other risk factors such as age, WBC count, and FAB (Franco-American-British) classification. (4 Refs)

13. CYTOGENETIC FEATURES OF HUMAN NEUROBLASTOMAS AND CELL LINES.

Brodeur GM, Green AA, Hayes FA, Williams KJ, Williams DL, Tsiatis AA
St. Louis Children's Hosp., 500 South Kingshighway Blvd., P.O. Box 14871, St. Louis, MO, 63178
Cancer Res; 41(11,part1):4678-4686 1981

We reviewed the banded karyotypes of 24 human neuroblastomas and cell lines to identify any consistent chromosomal abnormalities. Six of the 10 primary tumors and 1 of the 14 cell lines were studied at this institution. Of the 24 neuroblastomas karyotyped, 20 were near-diploid, 1 was near-triploid, and 3 were near-tetraploid. One primary tumor had a diploid karyotype without numerical or structural rearrangements. The 20 cases with a karyotype in the diploid range were statistically analyzed for gain or loss of whole chromosomes and for structural abnormalities of each chromosome arm. The short arm of chromosome 1 was preferentially involved in structural rearrangements, occurring in 14 cases (p less than 0.01). In 11 of these cases, the abnormality of chromosome 1 included deletion of bands 1p32--1pter, rendering the cells monosomic for this genetic material. Of the remaining three cases, one involved a reciprocal translocation of chromosomes 1p and 12q, another had insertion of genetic material at band 1p13, and the third had an extra dark band at 1p36. No other numerical or structural abnormalities occurred with sufficient frequency to reach statistical significance (p greater than 0.20). Six of the primary tumors or cell lines in the diploid range had double minute chromatin bodies, four cell lines had homogeneously staining regions, and two cell lines had either double minute chromatin bodies or homogeneously staining regions in subpopulations of cells. Hence, partial monosomy for the short arm of chromosome 1 was the most consistent cytogenetic abnormality in the human neuroblastomas studied. (Author abstract) (48 Refs)

14. GENETIC ETIOLOGY OF ESOPHAGEAL CANCER: II. CYTOGENETIC STUDIES ON PERIPHERAL BLOOD CELLS OF ESOPHAGEAL CANCER AND EPITHELIAL DYSPLASIA PATIENTS WITH POSITIVE FAMILY HISTORY IN LINXIAN COUNTY..

Wu Y, Ruan X

Cancer Inst., Chinese Acad. Medical, Beijing, People's Republic of China

Zhonghua Zhongliu Zazhi; 3(1):12-15 1981

Chromosome studies are described for 23 cases of untreated esophageal cancer (18 males, 5 females; aged 36-67 yr) and 20 case of untreated epithelial dysplasia (15 males, 5 females; aged 36-62) that had a positive family history of the disease. The control group consisted of 31 normal subjects (21 males, 10 females; aged 7-66 yr) from 'low risk' families that had no history of esophageal cancer for five generations. The metaphase of cultured peripheral blood lymphocytes from the three groups was examined for chromosome aberrations. Results showed that incidence of both numerical and structural chromosome aberrations were higher in the disease groups than in the control 'low risk' group. The numerical aberrations (greater than 2n) were 1.2%, and 3.2%. for esophageal cancer and epithelial dysplasia respectively as compared to 0.5% for the control; the structural aberrations were 1.94% and 2.94% for esophageal cancer and epithelial dysplasia as compared to 0.72% for the control. The findings suggest a relationship between chromosome aberrations and familial cancer occurrence in Linxian County. (4 Refs) (In CHI)

15. THE CLINICAL SIGNIFICANCE OF PH1 CHROMOSOME IN DISEASES OF HEMATOPOIETIC SYSTEM.

Qiu J, Zhang S, Gao X, Ruan H, Deng C
Tumor Res. Unit, Sichuan Medical Coll., Sichuan Province, People's Republic of China
Zhonghua Neike Zazhi; 20(3):170-172 1981

The Philadelphia (Ph1) chromosome has been observed in most chronic granulocytic leukemia patients and is useful in the diagnosis of this disease. Results of a cytogenetic study of 15 cases of diseases of the hematopoietic system are described. There were 10 males and 5 females, aged 15-64 yr. Among this series, 12 cases were chronic granulocytic leukemia, 2 cases were acute granulocytic leukemia and 1 case was secondary polycythemia vera. Emphasis is placed on the last three cases for which case reports are presented. The Ph1 chromosome was observed in the blood cells of all three cases. It was also observed in 11 of the 12 cases of chronic granulocytic leukemia (positive rate 91.7%). The appearance of the Ph1 chromosome and its value in the differential diagnosis of chronic granulocytic leukemia at its blastic phase from acute granulocytic leukemia are discussed. (14 Refs) (In CHI)

16. CHROMOSOME INSTABILITY IN PATIENTS WITH MEDULLARY CARCINOMA OF THE THYROID.

Hsu TC, Pathak S, Samaan N, Hickey RC
M. D. Anderson Hosp. and Tumor Inst., Texas Medical Center, 6723 Bertner Ave., Houston, TX, 77030
JAMA; 246(18):2046-2048 1981

Chromosome analysis in the cultured peripheral blood lymphocytes of multiple endocrine adenomatosis (MEA-II) patients and their siblings demonstrated a preponderance of higher frequency of metaphases with chromosome and chromatid type abnormalities (av, 11.0%) as compared to controls (av, 3.8%). Our preliminary data suggest that MEA-II patients exhibit some degree of chromosome instability. (Author abstract) (8 Refs)

17. CHROMOSOMAL BANDING PATTERNS IN HUMAN LARGE BOWEL CANCER.

Reichmann A, Martin P, Levin B
Dept. Medicine, Section Gastroenterology, Univ. Chicago, Box 400, 950 East 59th St., Chicago, IL, 60637
Int J Cancer; 28(4):431-440 1981

Cytogenetic banding studies were performed on direct preparations from 31 large bowel tumors. Twenty-eight of these were from primary sites and three from metastases. Some distinctive patterns were observed. The 31 tumors were separable into four groups: (1) Tumors with normal karyotypes (3 cases); (2) tumors with simple gains of chromosomes (3 cases); (3) tumors with gains, losses and structural aberrations (10 cases). Groups 1, 2 and 3 were all in the diploid range; and (4) tumors with hypotriploid-hypotetraploid karyotypes (15 cases). Nonrandom gains of several chromosomes, especially Number 8 and non-random losses of Number 17 were seen in this series. Thirteen cases had sex chromosome abnormalities. The most prominent structural abnormalities involved chromosomes Number 1 and Number 5. Marker chromosomes were sometimes absent, but when present ranged from simple translocations to the most complex rearrangements. Doubling of chromosome and/or marker chromosomes were prominent in Group 4. Double minutes were seen in all three metastatic tumors and three primary cancers. Premature chromosome condensation was observed in three cases in the hypotriploid-hypotetraploid group. (Author abstract) (40 Refs)

DNA CONTENT AND PLOIDY CHANGES ASSOCIATED WITH CANCER

18. HETEROCHROMATIN POLYMORPHISM OF A1 CHROMOSOME IN PATIENTS WITH OVARIAN CARCINOMA.

Adomat W, Weise W
Landesfrauenklinik der Medizinischen Akademie Magdeburg, Gerhart-Hauptmann-Str. 35, DDR-3010 Magdeburg, E. Germany
Zentralbl Gynaekol; 103(15):865-873 1981

Studies conducted by Atkin and Pickthall are likely to suggest more frequent occurrence in normal cells of enlargement of the heterochromatin region of the A1 chromosome in patients with ovarian carcinoma, and it is also claimed to be a predisposing factor, in the context of ovarian carcinoma. - The authors of this paper have tried to find out, if they could draw similar conclusions from their own patients and, therefore, applied cytogenetic tests of lymphocytes to 50 patients, including 25 who had undergone treatment for ovarian carcinoma and 25 control probands. - An assessment was made of 298 mitoses. C-bands were accurately measured and calculated in 84 mitoses of both groups. - The dimensions of A1 heterochromatin were variable in the authors' preparations, too. However, such variability in size in either group is considered still as normal variant of the well-known A1 polymorphism, and the authors were not convinced that pathognomonic relevance should be attributed to those findings. - Enlarged C-band of A1 chromsome was recordable only from one lymphocyte culture of one patient with ovarian carcinoma. C-banding, consequently, cannot be considered a suitable screening method for ovarian carcinoma, in the context of lymphocyte culturing. (Author abstract) (10 Refs) (In GER)

19. EFFECT OF PREOPERATIVE CHEMOTHERAPY ON DNA LEVEL IN SEROUS CYSTADENOCARCINOMA OF OVARIES.

Irzhanov SI, Serov SF
Municipal Oncological Dispensary, Leningrad, USSR
Vopr Onkol; 27(8):49-52 1981

The DNA level was determined cytophotometrically in 74 cases of cystadenocarcinoma of ovaries. Eighteen patients were not given a preoperative course of chemotherapy, while the rest received thioTEPA (triethylene thiophosphoramide) and cyclophosphamide. Changes in the DNA level and the distribution of ploidy may be used to assess tumor responsiveness to chemical drugs. (Author abstract) (13 Refs) (In RUS)

CHROMOSOMAL FRAGILITY AND GENETIC FACTORS PREDISPOSING TO HUMAN CANCER

20. POLYMORPHIC DIFFUSE B-CELL HYPERPLASIAS AND LYMPHOMAS IN RENAL TRANSPLANT RECIPIENTS.

Frizzera G, Hanto DW, Gajl-Peczalska KJ, Rosai J, McKenna RW, Sibley RK, Holahan KP, Lindquist LL
Univ. Minnesota, Mayo Memorial Building, Box 609, 420 Delaware St., South East, Minneapolis, MN, 55455
Cancer Res; 41(11,part1):4262-4279 1981

The lymphoproliferative processes that developed in five renal transplant recipients were studied in an attempt to characterize and classify them morphologically. Nine surgical specimens, hematological material on all patients, and autopsy specimens from three patients were available. Studies performed included: conventional histopathology; evaluation of cell markers (Ig and sheep RBC, complement, and Fc receptors) and cytoplasmic Ig (peroxidase-antiperoxidase technique); ultrastructural examination; and karyotype analysis. The lymphoid lesions in our patients shared marked cytological polymorphism (small and large cells, of both follicular center and 'medullary' type) and polyclonal B-cell features, which indicated a common reactive nonneoplastic origin. However, other features, such as morphological atypia of the immunoblasts, extensive necrosis, chromosomal aberrations, and an incipient monoclonal component suggested the development of lymphoma in some of these lesions. In contradistinction, the abundance of typical immunoblasts was a feature that seemed to correlate with the clinical activity of the disease rather than with the biological malignancy. The multiplicity of B-cell types and the presence of a follicular center cell component with diffuse distribution, as well as the extensive necrosis in the malignant forms, seem to differentiate morphologically the lymphoproliferative processes arising in transplant recipients from both the hyperplasias and the lymphomas developing in immunologically normal hosts. For the former, we propose the terms of 'polymorphic diffuse B-cell hyperplasias' and 'polymorphic B-cell lymphomas. (Author abstract) (45 Refs)

21. CLINICAL SPECTRUM OF LYMPHOPROLIFERATIVE DISORDERS IN RENAL TRANSPLANT RECIPIENTS AND EVIDENCE FOR THE ROLE OF EPSTEIN-BARR VIRUS.

Hanto DW, Frizzera G, Purtilo DT, Sakamoto K, Sullivan JL, Saemundsen AK, Klein G, Simmons RL, Najarian JS
Dept. Surgery, Univ. Minnesota, Mayo Memorial Building, 420 Delaware St. South East, Minneapolis, MN, 55455
Cancer Res; 41(11,part1):4253-4261 1981

Six renal transplant recipients with abnormal lymphoproliferative disorders were studied in an attempt to define their clinical features and the role of Epstein-Barr virus (EBV) in their pathogenesis. Patients were either teenage (3) or in the sixth decade (3). The younger patients presented an av of 3 mo after transplantation with fever, sore throat, and lymphadenopathy; had been markedly immunosuppressed; frequently had preceding or concomitant cytomegalovirus infections; and two of three had a rapidly fatal course. The older patients presented an av of 5 yr after transplantation while on maintenance immunosuppressive drugs; in two of three cases with an oropharyngeal tumor; and had a more indolent, but frequently fatal, clinical course. The most frequent sites of biopsy-proven involvement in these patients were lymph nodes (3), the oropharynx (3), liver (3), bone marrow (3), transplanted kidney (3), colon (2), and central nervous system (2). EBV-specific antibody titers including anti-viral capsid antigen IgG, anti-viral capsid antigen IgM, anti-early antigen, and anti-Epstein-Barr nuclear antigen were serially measured in all patients. Four patients demonstrated serological evidence of a primary (1) or reactivation (3) EBV infection. No patient had significant changes in anti-early antigen or anti-Epstein-Barr nuclear antigen titers. All three patients tested for oropharyngeal shedding of EBV were positive. A touch imprint of one tumor was stained for the presence of Epstein-Barr nuclear antigen, and a majority of cells were positive. EBV complementary RNA/DNA filter hybridization and/or viral DNA/DNA reassociation analysis performed on tumor biopsy specimens in five patients demonstrated multiple EBV genome equivalents per cell in all eight specimens tested. Clinical, pathological, serological, and molecular hybridization studies provide substantial evidence that EBV was the cause of these lymphoproliferative disorders occurring after renal transplantation. Impaired host defenses allow the EBV-transformed B-lymphocytes to escape normal control mechanisms. This impairment is variable and influenced by many factors resulting in the observed spectrum of disease. Cytogenetic changes, however, may also be important. (Author abstract) (45 Refs)

22. MONOSOMY 7 IN CHILDHOOD: A MYELOPROLIFERATIVE DISORDER.

Sieff CA, Chessells JM, Harvey BA, Pickthall VJ, Lawler SD

Dept. Haematology and Oncology, Hosp. Sick Children, Great Ormond St., London WC1N 3JH, England

Br J Haematol; 49(2):235-249 1981

Between 1976 and 1979 a myeloproliferative disease associated with cells monosomic for chromosome number 7 in the bone marrow was seen in six boys aged 5 1/2 mo to 8 yr (median 10 mo). Presenting features included hepatosplenomegaly (5/6), respiratory infections (4/6), pallor (2/6) and skin infections (1/6). Hematological features included a leukoerythroblastic anemia with leukocytosis and thrombocytopenia, and a hyperplastic marrow with a slight excess of blasts. Fetal Hb was normal in four patients and mildly raised in the other two. Neutrophil function tests showed defective chemotaxis with reduced killing, despite a normal NBT test. Cytogenetic analysis of the marrow showed a preponderance of cells with monosomy 7; the blood lymphocytes were cytogenetically normal. In three patients the disease progressed to acute myeloid leukemia (AML) after 3 wk to 23 mo; the only patient who remitted did so in response to 6-mercaptopurine and prednisolone, but relapsed 16 mo later. A fourth child developed massive splenomegaly which initially responded to 6-mercaptopurine and prednisolone, but progressed to myelofibrosis 11 mo later. A fifth child died from anemia and respiratory infection without progression to leukemia and the sixth patient has not yet developed leukemia. Monosomy 7 is the diagnostic criterion of one of the more common myeloproliferative states in childhood and carries a high risk of progression to AML. The acute phase is usually resistant to chemotherapy, but even in responsive cases treatment does not result in elimination of the abnormal clone. Allogeneic bone marrow transplantation should be considered in cases with a suitable donor. (Author abstract) (19 Refs)

23. SISTER-CHROMATID EXCHANGES IN LYMPHOCYTES IN WOMEN WITH CANCER OF THE BREAST.

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Dept. Anesthesia, Gentofte Hosp., DK-2900 Hellerup, Copenhagen, Denmark
Mutat Res; 85(5):357-362 1981

Sister chromatid exchanges (SCE) were studied in peripheral blood lymphocytes of 131 patients (17-90 yr old; median 51.8 yr) treated surgically for tumor of the breast. In 52 patients with perioperative histological proof of carcinoma of the breast, the SCE rate (mean +- standard error of the mean) was 9.39 +-0.17; the rate was 9.88 +-0.18 for 79 patients with nonmalignant fibroadenomatosis. Benign or malignant character of the tumor apparently did not influence SCE rate; age, preoperative mammography, and use of oral contraceptives or estrogens also were without significant influence. A statistically significant correlation was found between SCE and cigarette smoking. The 45 cigarette smokers exhibited 10.49 +-0.23 SCE/cell compared with 9.26 +-0.13 SCE/cell found in 86 nonsmoking patients. It is concluded that spontaneous SCE in lymphocytes is not an indicator of carcinoma of the breast. (19 Refs)

24. DICENTRIC Y CHROMOSOME IN A PATIENT WITH GONADAL DYSGENESIS AND SEMINOMA.

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(c/o Carbonara), via Santena 19, Torina, Italy
Hum Genet; 58(3):282-284 1981

The clinical, cytogenetic, and H-Y antigen features of a case of dicentric Y, [dic(Y)] with rudimentary gonad affected by malignant transformation is described. A 38-yr-old male underwent endocrinological studies following the appearance of bilateral gynecomastia. Hypospadias and labioscrotal folds present at birth had been partially corrected by surgery. No gonads were palpable. At 36 yr of age, the patient had undergone surgery for a seminoma of the left inguinal region. On presentation exploratory laparotomy was performed and showed a small uterus with streak gonad and a fallopian tube on the right and a rudimentary broad ligament without fallopian tube on the left. Hypergonadotropinemia and trace amount of testosterone indicated the absence of functional gonadal tissue. Sex chromatin was absent, and fluorescent Y bodies were detected in 30% of hair root cells. Chromosome studies showed a complex mosaicism with large proportion of 45,X and 46,Xdic(Yq) cell lines and a minor population with two dicentric Ys. After separate absorptions of anti-H-Y serum with the leukocytes and the red cells of the propositus, both kinds of cells tested H-Y positive. The significance of these results is discussed in relation to recent data on the genetic control of H-Y antigen. (11 Refs)

25. THE POSSIBILITY OF IN VITRO DETECTION OF INCREASED GENETIC RISK FOR PANCREATIC CANCER.

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Med Hypotheses; 7(9):1113-1116 1981

The identification of in vitro markers in subjects at risk for pancreatic cancer (PC) is discussed. In vitro studies done in several laboratories have demonstrated that monolayer cultures derived from skin biopsies from affecteds and some at-risk members of families with heritable colon cancer syndromes show cellular abnormalities. The association of increased in vitro tetraploidy and a family history of different solid tumors has been observed. Three types of PC have been identified based on family pedigrees: PC with an autosomal dominant inheritance pattern, PC in association with other malignant neoplasms (cancer family syndrome), and PC in association with hereditary pancreatitis. The first two are believed to result from a germinal mutations. In the third case, PC may result as a complication of pancreatitis or as result of gene mutation. It has been proposed that cultured cells derived from an individual having an increased genetic risk for PC should demonstrate this predisposition by culture abnormalities. In one family with PC in two consecutive generations (I and II), 3/8 family members at risk in generation III and 1/3 members studied in generation IV showed increased in vitro tetraploidy. It must be determined if all clinically affecteds show the same in vitro abnormality and if vertical transmission of this marker in the pedigree can be documented. The role of in vitro PC markers in the identification of PC is discussed. (9 Refs)

CHROMOSOMES OF HUMAN CELL LINES AND TUMORS IN VITRO

26. A METHOD FOR OBTAINING HIGH QUALITY CHROMOSOME PREPARATIONS FROM SINGLE HEMOPOIETIC COLONIES ON A ROUTINE BASIS.

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Cancer Genet Cytogenet; 4(2):157-168 1981

The need for improved methodology to facilitate cytogenetic analysis of hemopoietic stem cell populations, particularly in studies of the hemopoietic malignancies, has been recognized for a number of yr. Since primitive hemopoietic cells can be stimulated to form colonies of identifiable progeny under appropriate conditions in vitro, it should in theory, be possible to obtain such information. However, hemopoietic colonies of human origin rarely contain more than 1,000 cells, and in handling such small samples, cell loss has historically been a major problem. We now describe a method that has allowed from two up to more than 50 metaphases per colony to be obtained from most erythroid and granulopoietic colonies harvested individually from standard methylcellulose assay cultures. Of key importance is the selection of large but still immature colonies and the use of polylysine coated slides, which ensures recovery of 80-90% of the sample. The method yields reproducibly high quality metaphases suitable for analysis after G, Q, and fluorescent-reverse banding. Cytogenetic analysis of 58 colonies removed individually from cultures initiated with a mixture of male and female cells showed both male and female colonies to be present as expected. In all instances only one type of metaphase was ever found in a single colony. A procedure for measuring the incidence of sister chromatid exchange (SCE) in the progeny of primitive hemopoietic progenitors has also been established. SCE values obtained for 1-to 2-wk-old colonies derived from normal progenitors were similar to previously published normal SCE values. Preliminary analysis of erythroid and granulocytic colonies from one patient with polycythemia vera (PV) and two patients with chronic myelogenous leukemia (CML) indicate that preparations of equal quality are obtained from such individuals and thus, for the first time, the Ph1 chromosome could be readily demonstrated in erythroid colonies. Further application of this method to the investigation of patients with myeloproliferative disease is now underway. (Author abstract) (34 Refs)

27. CHROMOSOME 14 MARKERS IN TWO EPSTEIN-BARR VIRUS (EBV)-TRANSFORMED LYMPHOBLASTOID CELL LINES OF NORMAL ORIGIN DIFFER FROM THE BURKITT LYMPHOMA (BL)-ASSOCIATED 14Q+ MARKER.

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Cancer Genet Cytogenet; 4(2):179-184 1981

Two among 10 Epstein-Barr Virus (EBV)-transformed lymphoblastoid cell lines contained a 14q+ marker in a low frequency of the cells (2 and 9%). By means of 'mesome-prosome' analysis of the G-band patterns of these markers; it was established that the additional chromosome segments of these two 14q+ markers came from chromosomes 3 and 5, respectively, and not from chromosome 8 as in the 14q+ marker of Burkitt lymphoma. Chromosome 8 was not involved at all in any changes in the 10 lymphoblastoid cell lines studied. (Author abstract) (19 Refs)

28. GROWTH CHARACTERISTICS OF HUMAN GLIOMA-DERIVED AND FETAL NEURAL CELLS IN CULTURE.

Icard C, Liepkalns VA, Yates AJ, Singh NP, Stephens RE, Hart RW
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J Neuropathol Exp Neurol; 40(5):512-525 1981

Growth characteristics of human fetal neural cells (CH) and human glioblastoma multiforme-derived cells (12-18) in culture were compared. Cells were grown to confluent densities of 38,000 to 42,500 cells/cm2 for CH and 85,800 to 87,100 for 12-18. Population doubling times were 40.0 +-5.1 hr and 66.5 +-9.8 hr for CH and 12-18 cells, respectively. The mean DNA content per cell of the glioma-derived cells was twice that of the fetal brain cells at sparse, log, and confluent cell densities. High concentrations (40%) of serum in growth medium increased DNA contents in confluent CH, but not 12-18, cells. The amount of protein per cell also was consistently higher in glioma cells than CH cells, but, as cell densities increased, protein contents decreased for both: 1200 to 700 pg/cell in glioma cells, and 840 to 560 pg/cell in CH cells. In each cell line, initial rates of [3H]ThdR incorporation into TGA precipitable material decreased as cell density increased, but confluent glioma-derived cells incorporated 10x more [3H]ThdR than confluent fetal cells. Almost all CH cells had a normal diploid chromosome number of 46. A histogram showing the relative frequencies of chromosome numbers of glioma-derived cells had peaks of 52, 79, and 105 chromosomes per metaphase, indicating a haploid number of 26 for most cells. Lengths of cell cycle phases, determined using autoradiographic techniques, indicate that glioma-derived cells had a longer generation time and S period than fetal neural cells. These data demonstrate several biological differences between glioblastoma-derived cells and non-neoplastic fetal neural cells, indicating that this system is of potential value for comparative studies on growth control and contact inhibition. (Author abstract) (31 Refs)

29. ESTABLISHMENT AND CHARACTERIZATION OF A CELL LINE (BR-NHF-1) DERIVED FROM HUMAN MAMMARY CARCINOMA.

Nomoto C, Suemasu K, Higashi Y, Takeuchi O, Shisa H, Tsuchiya S, Hozumi M, Yoshida S
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Gan; 72(5):783-789 1981

A new human cell line, Br-NHF-1, was established from the pleural effusion of a patient with advanced mammary carcinoma. The cells survived 52 subcultivations during more than 33 mo. The cells possess epithelial features, showing rosettes, acinar formation and domes in or among the compact colonies. The modal chromosome number is 51 with some marker chromosomes. Xenografted tumors retained a similar histology to the original tumor. No estrogen-binding protein was detectable in the culture, but there was a significant amount of basic fetoprotein. Production of casein in the cells was detected by immunofluorescence testing. (Author abstract) (22 Refs)

30. DIPLOID HUMAN LYMPHOBLASTOID AND BURKITT LYMPHOMA CELL LINES: SUSCEPTIBILITY TO MURINE NK CELLS AND HETEROTRANSPLANTATION TO NUDE MICE.

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Int J Cancer; 28(4):455-458 1981

Human lymphoid cell lines which had been classified on the basis of studies on clonality and morphological, chromosomal and functional parameters as lymphoblastoid cell lines (LCL) of presumed non-neoplastic origin and Burkitt lymphoma (BL) lines of proven malignant origin, were tested for susceptibility to natural killer (NK) cells obtained from the spleens of athymic nude mice. The 20 lines included normal diploid LCL and aneuploid BL lines. All cells carried the Epstein-Barr virus (EBV) genome. In addition, two EBV-negative BL lines were tested. The pronase-induced release of 14C-DNA from 14C-thymidine-lab eled target cells was used to assess the sensitivity of the cell lines to NK activity. When attempts were made to correlate the growth of the EBV-positive LCL and the EBV-positive BL cell lines in the sc space of adult nude mice with their susceptibility to NK cells, no significant correlation was observed. The EBV-negative BL cell line, Ramos, however, could be transplanted subcutaneously in nude mice and was more resistant to NK activity than was the EBV-negative BL cell line, BJAB, which cannot be transplanted subcutaneously. Growth of heterotransplanted EBV-converted cell lines in the sc space of adult nude mice may be influenced by immune effectors other than NK cells. (Author abstract) (23 Refs)

31. DEVELOPMENT OF RESISTANCE TO VINCRISTINE IN A CHILDHOOD RHABDOMYOSARCOMA GROWING IN IMMUNE-DEPRIVED MICE.

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Int J Cancer; 28(4):409-415 1981

A cell line of childhood rhabdomyosarcoma (RD) has been grown as a xenograft in immune-deprived mice. The tumor responded to vincristine (VCR), but not to vinblastine, doxorubicin or actinomycin D. The rate and frequency at which resistance developed from administration of VCR once weekly was investigated. Tumor growth could be inhibited for 6 wk, after which time 11 of 16 xenografts grew progressively despite continued treatment. That this was a tumor acquired resistance was confirmed by growing both parent and 'resistant' lines in the same host. Under these conditions VCR completely inhibited growth of the parent tumor, but not growth of the resistant line. Continued passage of the resistant line for 10 mo in mice either treated with VCR (1.5 mg/kg/wk) or untreated, demonstrated that resistance to VCR was stable in the absence of selection pressure. In addition, the VCR-resistant line acquired a stable change in karyotype with the addition of a number 9 chromosome and an additional, unknown marker. (Author abstract) (42 Refs)

32. SISTER CHROMATID EXCHANGE IN LYMPHOMA LINES AND LYMPHOBLASTOID CELL LINES BEFORE AND AFTER HETEROTRANSPLANTATION INTO NUDE MICE.

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Int J Cancer; 28(4):441-445 1981

The sister chromatid exchange (SCE) rates of cell lines derived from patients with different malignant and premalignant diseases were studied before and after intracerebral inoculation into nude mice and were compared to the SCE frequencies of cell lines from healthy controls. Lymphoma lines characterized by chromosomal markers as well as chromosomally normal lymphoblastoid cell lines were used. The SCE frequencies of nude mouse tumor-derived cell lines did not show a homogeneous pattern. They were either as high as, or higher or lower than, the SCE levels of the original cell line. But all cell lines, karyotypically abnormal as well as normal, originating from patients with malignant and premalignant diseases, showed significantly higher SCE rates than the control lines from healthy donors. (Author abstract) (10 Refs)

33. LYMPHOPROLIFERATION AND HETEROTRANSPLANTATION IN NUDE MICE: TUMOR CELLS IN HODGKIN'S DISEASE.

Diehl V, Kirchner HH, Schaadt M, Fonatsch C, Stein H
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Haematol Blood Transfus; 26:229-234 1981

Histologically proven Hodgkin's disease (HD) derived material was used to establish four long term cultures. These in vitro cells had morphologic, cytochemical and cytogenetic features of their in vivo ancestors. Two of these cultures were obtained from pleural effusions of HD nodular sclerosing type, Stage IV B (diagnosed, one in 1972 and another in 1976). They shared these same features: non-B-T lymphocytes, non-macrophages, non myeloid cells, Epstein-Barr virus genome negative, monoclonality, multiple numerical and structural chromosome aberrations, and tumor formation after intracranial xenotransplantation in nude mice. After sc inoculation both lines failed to induce tumors. When one of them was embedded in a fibrin clot prior to transplantation, infiltrative tumor growth resulted after sc inoculation. Morphology of the two cell lines was very similar to Hodgkin (H) and Sternberg-Reed (SR) cells. Biological and immunological characterization of the two lines showed identical pattern observed in freshly prepared H and SR cells. They resemble very closely cultured H cells described by Kaplan. (14 Refs)

CHROMOSOMES OF ANIMAL CELL LINES AND TUMORS

34. CHROMOSOMAL ALTERATIONS IN THE COURSE OF VIRAL LEUKEMOGENESIS IN THE RAT.

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Cancer Genet Cytogenet; 4(2):143-155 1981

A cytogenetic study of 35 primary thymic lymphomas induced in rats by the Gross leukemia virus revealed the presence of widespread aneuploidies, ranging from cells with 35 chromosomes or less to triploid and tetraploid cells. Analysis by G banding revealed that chromosomes No 1, 2, 9, 12, 18-20, X in females, and Y in males were lost preferentially; unidentified marker chromosomes of various morphology and length were present in a high percentage of aneuploid mitoses. Similar alterations were observed in preleukemic thymi from rats sacrificed 30 days after virus injection, when clinical or histologic signs of the disease had not yet appeared. In rats that were sacrificed 7 or 15 days after virus injection, chromosomal anomalies were much more limited, although significantly more abundant than in the controls. Rats that were free of tumor at 130-160 days after virus injection showed a regression of the chromosomal anomalies, suggesting that these are not irreversible and are not necessarily followed by the development of a lymphoma. (Author abstract) (31 Refs)

35. COINCIDENCE OF CYTOGENETIC MARKERS IN FOUR MURINE CELL LINES.

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Cancer Genet Cytogenet; 4(2):169-177 1981

Foreign body tumorigenesis was induced by the sc implantation of a plastic or glass cylinder in BALB/c mice; the inoculation of human neoplastic cells significantly increased the incidence of these anaplastic sarcomas. Of 15 tumors studied, 4 presented the same markers: 1 induced with and 3 without human neoplastic cell inoculation within the foreign body. The markers observed were double minutes (DM), a long acrocentric marker (MLA), and a metacentric marker (MM). The DM are a number of small often tiny chromosomal structures appearing in pairs together with chromosomes of ordinary size. MLA is a long acrocentric derived from a translocation in tandem between chromosomes No 1 and No 16. MM is due to centric fusion of two chromosomes No 10. Numerical anomalies consisted of gains of the same chromosome types. It is postulated that these coincident findings are related to the foreign-body tumorigenesis. (Author abstract) (23 Refs)

36. KARYOTYPES OF THE 5-AZACYTIDINE-SENSITIVE AND -RESISTANT LINE OF AKR MOUSE LEUKEMIA.

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Neoplasma; 28(3):317-323 1981

The karyotype of AKR mouse lymphoblastic leukemia cell line made resistant to 5-azacytidine was compared with the karyotype of the parental line. In relation to 5-azacytidine-resistant line the parental cells have less chromosome No 5 and more of No 17 per karyogram. The increased monosomy has been found in chromosomes No 5, 6, 7, 8 and 18 in sensitive line and in chromosomes No 1, 8 and 17 in 5-azacytidine-resistant cells. The highest occurrence of trisomy was present in the chromosomes No 13 and 16 in both lines. In AKR sensitive cells 89% of karyograms displayed 3 to 13 markers per karyogram while in the resistant line there were only 37% of karyograms with 1 to 11 markers. (Author abstract) (34 Refs)

37. CYTOGENIC STUDIES OF SHAY'S GRANULOCYTIC SARCOMA BY BAND STAININGS.

Asano Y
Second Dept. Internal Medicine, Showa Univ. Sch. Medicine, Tokyo, Japan
Nippon Ketsueki Gakkai Zasshi; 44(5):998-1006 1981

Chromosomal analysis of Shay's granulocytic sarcoma was first carried out by Nowell et al in 1961. Shay's granulocytic sarcoma has been maintained by sc inoculation in our laboratory since 1963. T H Yoshida and T Sakai observed chromosomal alterations in this tumor during the 35th to 179th transplant generations. The present study deals with the banding pattern analysis during 335th to 344th transplant generations. The stemline cells of this tumor showed 43 chromosomes with one small subtelocentric extra chromosome and three marker chromosomes, in which one long telocentric (No 4), one medium submetacentric (No 10), and one long subtelocentric chromosome (No 13) were involved. G, Q and C banding techniques revealed the origin of four marker chromosomes. No 4 chromosome was caused by duplication, No 10 chromosome by pericentric inversion and No 13 chromosome by translocation between No 2 chromosome and No 13 chromosome in the course of serial transplantation. It was confirmed that extra chromosome had originated from breakage of one chromosome among No 3 trisomy. (Author abstract) (29 Refs) (In JPN)

GENE MAPPING STUDIES

38. EXPRESSION OF CHRONIC MYELOID LEUKAEMIA-ASSOCIATED CHANGES IN MEMBRANE GLYCOPEPTIDES IN SOMATIC CELL HYBRIDS.

Geurts van Kessel AH, Smets LA, Van Rooy H, Hagemeijer A
Dept. Cell Biology and Genetics, Erasmus Univ., Rotterdam, The Netherlands
J Cell Sci; 51:121-130 1981

Hybrid cell lines, derived from fusion of rodent cells with peripheral WBC from patients with chronic myeloid leukemia (CML) and from normal donors, were assayed for the presence of CML-associated changes in the carbohydrate moieties of membrane glycoproteins. Expression of this characteristic phenotype did occur in several hybrid clones derived from fusions both with leukemic and normal human WBC. But, expression was only observed when tumorigenic rodent cells were used as fusion partners, and was not observed after fusion with non-tumorigenic rodent cells. Chromosome analysis of the hybrid cells did not reveal a single human chromosome- or chromosomal aberration (eg the Philadelphia chromosome)-bearing factor(s) responsible for this expression. The phenotypic expression observed could be due to dissociation of certain human genes from their regulator(s), as a result of chromosome loss in interspecific cell hybrids. (Author abstract) (19 Refs)

39. USE OF WHOLE-CELL FIXATION TO VISUALIZE REPLICATING AND MATURING SIMIAN VIRUS 40: IDENTIFICATION OF NEW VIRAL GENE PRODUCT.

Jackson V, Chalkley R
Dept. Biochemistry, Sch. Medicine, Univ. Iowa, Iowa City, IA, 52242
Proc Natl Acad Sci USA; 78(10):6081-6085 1981

Formaldehyde fixation of simian virus 40 (SV40)-infected CV-1 cells at appropriate times after infection permits us to isolate crosslinked complexes of SV40 minichromosomes during the time of DNA replication and during packaging with viral proteins. Such crosslinked complexes can be separated on the basis of density on CsCl/guanidine.HCl density gradients. During the course of these studies we observed the presence of a low mol wt protein in a region of the gradient much enriched with viral nucleoproteins. This protein is present only in infected cells and has a mol wt and amino acid composition consistent with it being the product of the so-called SV40 agnogene. (Author abstract) (21 Refs)

40. PREFERENTIAL ASSOCIATION OF URACIL-DNA GLYCOSYLASE ACTIVITY WITH REPLICATING SV40 MINICHROMOSOMES.

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FEBS Lett; 133(1):89-91 1981

The preferential association of a major DNA repair enzyme, uracil-DNA glycosylase, with replicating SV40 minichromosomes in investigated. A nuclear extract containing SV40 minichromosomes, but free of cellular DNA and mitochondria was centrifuged to separate replicating and mature minichromosomes. Uracil-DNA glycosylase was tested by collecting fractions from the nuclear extract and incubating with an assay buffer and d3H uracil monophosphate (dUMP) containing DNA. The release of acid or ethanol soluble radioactivity was monitored. Cytochrome c oxidase was determined in aliquots of 100 ul from extracts or gradient fractions. To label both replicating and mature SV40 chromatin, SV40 infected CV-1 cells were incubated with 14C thymidine. Nuclear extracts were prepared as above. Uracil-DNA glycosylase activity was measured in each fraction. Results showed that uracil-DNA glycosylase cosediments with replicating chromatin; a smaller fraction cosedimented with mature chromatin. Thin layer chromatography of the ethanol soluble radioactivity released showed 90% comigrated with uracil. No cytochrome c oxidase activity cosedimented with SV40 minichromosomes. Apparently cosedimentation of uracil-DNA glycosylase with replicating chromatin is not due to contamination by mitochondria. The results suggest that uracil-DNA glycosylase is preferentially associated with replicating SV40 minichromosomes. This may indicate that misincorporation of dUMP is a more frequent event than cytosine deamination. (24 Refs)

41. GENETICS OF SUSCEPTIBILITY TO RADIATION-INDUCED LEUKEMIA. MAPPING OF GENES INVOLVED TO CHROMOSOMES 1, 2, AND 4, AND IMPLICATIONS FOR A VIRAL ETIOLOGY IN THE DISEASE.

Meruelo D, Offer M, Flieger N
Irvington House Inst., New York Univ. Medical Center, New York, NY, 10016
J Exp Med; 154(4):1201-1211 1981

The genetics of susceptibility to radiation-induced leukemia in (A/J x B10)F2 mice were defined and the genes involved were localized. A major locus conferring resistance to fractionated irradiation (Cs-137; 180 rad/wk for 4 wk) induction of leukemia was mapped in chromosome 2 (Ril-1). Loci next to xenotropic murine leukemia virus (MuLV) envelope-related cell-surface antigens (XenCSA) on chromosome 4 (Ril-3) and Pep-3 on chromosome 1 (Ril-2) also influenced susceptibility to the leukemia. Leukemia incidence on day 250 after last irradiation was 86% and 90% in mice lacking the phenotypes Ly-6.2 or Ly-11.2, respectively, on chromosome 2. Effects related to genes linked to Ly-15.2R and Pep-3 loci were less important: the number of phenotype-nonleukemic animals 300 days after irradiation were 29% (phenotype 15.2/15.2) and 15% (Pep-3 phenotype AA). Ril-1 is located in a chromosomal site rich in thymus differentiation-specific loci; a linkage of Ril-1 and Ly-11 suggests that this region of chromosome is not silent to the inductive effects of fractionated irradiation. Tissue-specific activation of endogenous viruses may be explained by dependency on differentiation-specific steps. (40 Refs)

42. FV-4: GENE CONTROLLING RESISTANCE TO NB-TROPIC FRIEND MURINE LEUKEMIA VIRUS. DISTRIBUTION IN WILD MICE, INTRODUCTION INTO GENETIC BACKGROUND OF BALB/C MICE, AND MAPPING OF CHROMOSOMES.

Odaka T, Ikeda H, Yoshikura H, Moriwaki K, Suzuki S

Inst. Medical Science, Minato-ku, Shirokanedai 4-6-1, Tokyo 108, Japan

JNCI; 67(5):1123-1127 1981

A gene controlling resistance to NB-tropic Friend murine leukemia virus (F-MuLV) was studied in wild mice. Mice of various subspecies were crossed with inbred BALB/c mice, and their F1 hybrids were tested for resistance to F-MuLV. Some mice of Mus musculus molossinus (Japan), M musculus castaneus (Taiwan and the Philippines), and M musculus urbanus (Sri Lanka) appeared to have the dominant resistance gene. A partially congenic strain, BALB/c-Fv-4wr (C4W), was established by the introduction of the gene Fv-4wr from a M musculus molossinus into the genetic background of BALB/c mice. [(C4W x DBA/2) x C57BL/6-Fvs] crosses revealed that Fv-4wr is located on chromosome 12 with the gene order of Fv-4w-Pre-1-Igh-1, apparently at the same site as the Fv-4. The resistance of C4W mice was indistinguishable from the Fv-4-controlled resistance of FRG mice. (Author abstract) (22 Refs)

43. MICROINJECTION OF CLONED RETROVIRAL GENOMES INTO MOUSE ZYGOTES: INTEGRATION AND EXPRESSION IN THE ANIMAL.

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Nature; 293(5833):540-542 1981

Cloned genomic retroviral DNA is expressed in mouse zygotes after microinjection. The resulting virus integrated into the mouse genome at a single chromosomal site and was expressed in a tissue-specific manner. Our findings suggest that the chromosomal position of a viral genome influences its activation during development. (Author abstract) (22 Refs)

MOLECULAR CYTOGENETICS

44. KAPOSI'S SARCOMA. IV. DETECTION OF CMV DNA, CMV RNA AND CMNA IN TUMOR BIOPSIES.

Boldogh I, Beth E, Huang ES, Kyalwazi SK, Giraldo G

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Int J Cancer; 28(4):469-474 1981

In order to determine whether human cytomegalovirus-(CMV) DNA homologous sequences as well as CMV-specific RNA(s) and antigen(s) exist in tumor biopsies of Kaposi's sarcoma (KS), DNA-DNA reassociation, RNA-DNA in situ cytohybridization and anticomplement immunofluorescence test (ACIF) tests were applied. Three of 10 DNAs extracted from Kaposi sarcoma biopsies contained DNA sequences homologous to radioactively labeled human CMV DNA probe. The amount of CMV DNA in these sarcoma tissues was calculated to range from 0.7 to 1 genome equivalent per diploid cell. The presence of virus-specific RNA was also demonstrated in sections from 5 of 10 tumor biopsies. CMV-determined nuclear antigen(s) (CMNA) present in variable degrees were also demonstrated. In contrast, we could not detect any herpes simple virus type II (HSV-2) or Epstein-Barr virus (EBV) DNA sequences in DNA of these tumor biopsies. Furthermore, there were no detectable HSV-2 or EBV-specific RNA or virus-specific antigens in sections of these biopsies. These results provide new lines of evidence for the relationship between CMV and Kaposi's sarcoma. (Author abstract) (34 Refs)

45. MULTIPLE IMMUNOGLOBULIN SWITCH REGION HOMOLOGIES OUTSIDE THE HEAVY CHAIN CONSTANT REGION LOCUS.

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Lab. Molecular Genetics, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20205

Nature; 293(5833):585-587 1981

Using the switch segment as a hybridization probe, switch-like regions in germ-line DNA were studied. The effect of the mu-alpha switch on these switch-like regions in the IgA-producing plasmacytoma cell line S107 was determined. The heavy chain regions of the S107 cells were studied. Maps are presented of germ-line mouse mu and alpha S107 rearranged alpha genes, constructed from cloned DNA fragments from partial restriction endonuclease digests of total mouse 12-day-old embryo or S107 DNA using circular DNA and genomic probes. Hybridization of mouse embryo and S107 cell line DNA to probes from the immunoglobulin heavy chain locus is described. Autoradiographic studies indicated that on both chromosomes in S107, rearrangement occurred which deleted the entire region between the mu switch and the alpha switch. Rearrangeable DNA fragments in mouse embryo and three myeloma cell line DNAs are presented. The results indicate that approx 15 switch-like regions are present in germ line DNA and that only one is deleted during the mu-alpha switch occurring in the IgA-producing cell line S107. As the heavy chain constant region locus from mu through epsilon was deleted in this cell line (including all the other known heavy chain genes), it seems that the remaining switch-like signals lie outside this region. (36 Refs)

46. STRUCTURE OF A CHROMOSOMAL GENE FOR HUMAN INTERFERON BETA.

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Proc Natl Acad Sci USA; 78(9,part2):5305-5309 1981

We have cloned and analyzed a chromosomal DNA segment containing the human interferon beta1 gene from a human gene library. The nucleotide sequence of the protein-coding and the noncoding regions of the chromosomal gene was identical to the cDNA sequence reported previously. In the region upstream from the putative transcription initiation site, significant nucleotide sequence homology was observed between interferon beta1 and alpha1 genes. This region thus may play a role in expression of the interferon genes. From the sequence data and the result of nuclease S1 mapping experiments, we conclude that, like the interferon alpha1 gene, the interferon beta1 gene is devoid of intervening sequences. (Author abstract) (40 Refs)

47. PLASMACYTOMAS WITH MORE THAN ONE IMMUNOGLOBULIN 5K 1 MRNA: IMPLICATIONS FOR ALLELIC EXCLUSION.

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Proc Natl Acad Sci USA; 78(9,part2):5812-5816 1981

Although only one allele of an Ig gene is thought to be expressed as a polypeptide by a given lymphocyte ('allelic exclusion'), three murine plasmacytomas were found to contain more than one kappa light chain mRNA species, as evidenced by the sequences of distinct kappa cDNA clones. Two different kappa cDNA sequences were cloned from BFPC 61 microsomal mRNA, two from MOPC 173, and three from S107. One cDNA sequence from each tumor matches the known secreted polypeptide, while the variant sequences differ in the variable (V) region. Hence fusion of a Vkappa gene to a joining (Jkappa) gene has occurred independently on separate homologous chromosomes and each allele is transcriptionaly competent. The BFPC 61 variant sequence contained a normal Vkappa sequence linked out of phase to Jkappa2; hence allelic exclusion in this line is accounted for by an error in DNA rearrangement. One S107 variant cDNA has an untranslatable sequence linked to Jkappa-Ckappa and may derive from a non-Vkappa or pseudo-Vkappa gene fused to Jkappa. Another S107 variant cDNA, however, has a proper Vkappa linked in phase to Jkappa (albeit missing the first two germ-line Jkappa codons) and the MOPC 173 variant sequence also contains a proper Vkappa linked in phase to Jkappa (albeit missing the first 2 germ-line Jkappa codons) and the MOPC 173 variant sequence also contains a proper Vkappa-Jkappa join, although it does not encode a tryptophan residue common to all Ig chains. The presence of two potentially expressible kappa mRNAs in both S107 and MOPC 173 suggests that allelic exclusion does not hold in all lymphocytes, or that it sometimes reflects events subsequent to mRNA production, such as inability of certain kappa chains to assemble properly with the heavy chain. These observations are compatible with a stochastic model for allelic exclusion in which productive and nonproductive V-J recombination events occur at a certain frequency for each allele. (Author abstract) (44 Refs)

EFFECTS OF EXOGENOUS AGENTS ON CHROMOSOMES

48. XERODERMA PIGMENTOSUM AND MEDULLOBLASTOMA: CHROMOSOMAL DAMAGE TO LYMPHOCYTES DURING RADIOTHERAPY.

Giannelli F, Avery J, Polani PE, Terrell C, Giammusso V

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Radiat Res; 88(1):194-208 1981

The response of a xeroderma pigmentosum (XP) patient to radiotherapy for medulloblastoma (MB) was evaluated in terms of clinical and cytogenetic observations. Two other children with MB alone were treated similarly on the linear accelerator following surgery. Treatment was started to the whole cranium, reduced to cover the posterior fossa and pituitary region, and then finally reduced to cover the posterior fossa alone. The dose to the posterior fossa was the highest (5,000-5,500 rad). In the two MB patients, spinal radiation was not begun until 2,000-2,500 rad of cranial radiation had been administered, while in the XP patient, spinal irradiation was begun immediately. Mild radiation erythema was observed in all three patients at the end of radiotherapy. The total WBC and platelet counts of the XP patient did not at any time fall too low for daily treatment as they did in the Asian MB patient. The XP patient was alive and neurologically well 2.5 yr after treatment. At the end of treatment, the chromosome aberrations per rad were lowest in the XP patient and highest in one of the MB patients. Results indicated that the number of chromosome aberrations is much better correlated to spinal than cranial irradiation doses. It was suggested that since the XP patient had received treatment most damaging to lymphocytes (spinal radiation) partly at the beginning and partly at the end of radiotherapy, the final chromosome damage may be lower since a great proportion of the damaged cells may have been lost during therapy. The results of this study indicated that radiotherapy administered to XP patients does not produce high frequencies of damaged lymphocytes, high levels of chromosome aberrations per cell, nor clinically abnormal reactions. (30 Refs)

49. STUDIES ON OSTEOPOROSIS. V - COMPARISON OF METHODS OF EVALUATION OF OSTEOPOROSIS AND STUDY OF CHROMOSOME CHANGES INDUCED BY NEUTRON ACTIVATION.

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J Med; 12(4):251-256 1981

In vivo activation analysis was compared with ashing and atomic absorption spectrophotometry for the determination of total skeletal calcium content in mice. The results were close to identical. The possible mutagenic-carcinogenic effect of repeated exposure to whole body neutron irradiation was studied by chromosome analysis. Under the conditions of these experiments, no significant chromosome changes were seen. (Author abstract) (6 Refs)

50. SISTER CHROMATID EXCHANGES (SCE) AND CHROMOSOMAL ABERRATIONS OF CULTURED CELLS OF MOUSE EMBRYO INDUCED BY IONIZING RADIATION AND CHEMICAL CARCINOGEN.

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Dept. Biological Effect of Radiation, Lab. Industrial Hygiene, Ministry of Public Health, Beijing, People's Republic of China
Acta Anat Sin; 12(2):220-224 1981

The effects of 60Co-gamma rays and benzopyrene in the induction of SCE and chromosome aberrations are described for cultured murine embryo cells. At a dose level of 300 rad, 60Co-gamma rays induced 1.3 and 24 times more SCE and chromosome aberrations respectively than the unirradiated controls, while a dose of 50 rad produced no difference. At a dose of 0.05 ug per ml of culture media, benzopyrene increased the frequency of SCE by about 1.8 times that of the control while no change in chromosome aberrations was observed. The significance of SCE and chromosome aberrations in the evaluation of carcinogens in discussed. (12 Refs) (In CHI)

51. CYTOCHALASIN B INDUCES ABNORMAL CHROMOSOME SEGREGATION IN FRIEND ERYTHROLEUKAEMIA CELLS.

McMenamin M, Hickey I
Sub-Dept. Genetics, Queen's Univ., Belfast BT7 1NN, Ireland
Eur J Cell Biol; 25(1):215-217 1981

Friend erythroleukemia cells were made binucleate by brief exposure to cytochalasin B (CB). The binucleate cells were then allowed to grow in the absence of CB. They produced pseudotetraploid derivatives which subsequently showed considerable variation in chromosome number. Cells with abnormal chromosome numbers failed to form clones, and disappeared from the culture. This is in marked contrast to previously reported stable pseudotetraploid cells arising in baby hamster kidney cells after CB treatment. (Author abstract) (6 Refs)

52. POTENCY OF SOME CARBAMATES AS MULTIPLE TISSUE SISTER CHROMATID EXCHANGE INDUCERS AND COMPARISON WITH KNOWN CARCINOGENIC ACTIVITIES.

Cheng M, Conner MK, Alarie Y
(c/o Conner) Dept. Industrial Environmental Health Sciences, Graduate Sch. Public Health, Univ. Pittsburgh, Pittsburgh, PA, 15261
Cancer Res; 41(11,part1):4489-4492 1981

The ethyl, ethyl N-hydroxy, isopropyl, and methyl esters of carbamic acid were examined for their abilities to induce sister chromatid exchanges (SCEs) in alveolar macrophages, bone marrow, and regenerating liver cells of C57BL/6J x DBA/2J F1 mice. The relative potencies in inducing SCE, ethyl greater than ethyl N-hydroxy- greater than isopropyl, paralleled previously described activities for induction of lung adenomas in strain A mice. The noncarcinogenic methyl carbamate was inactive in the SCE assay. Relative to bone marrow, regenerating liver and alveolar macrophage cells demonstrated increased susceptibility to carbamate-induced SCE. Of all carbamates studied, only the directly active compound, ethyl N-hydroxycarbamate, produced distinctly different responses in extrahepatic tissues of hepatectomized and intact mice. In intact mice, SCE levels induced by ethyl carbamate in bone marrow and alveolar macrophage cells were not significantly different whether assay followed the last of 12 (3x weekly) serial injections of 2.2 mmol/kg each or after a single injection of 2.2 mmol/kg. Linear regression relationships of log ethyl carbamate versus log SCE or log adenoma response were found to be parallel with the two assays having similar sensitivities. (Author abstract) (21 Refs)

53. EFFECTS OF 1-BETA-D-ARABINOFURANOSYLCYTOSINE ON CHROMOSOMES, DEPENDING UPON THE CELL CYCLE STAGE AT THE TIME OF EXPOSURE.

Moore RC
Biological Res. Unit, Cancer Inst., 481 Little Lonsdale St., Melbourne 3000, Australia
Mutat Res; 83(3):361-374 1981

JU56 cells, derived from the black-tailed wallaby, were exposed to 1-beta-D-arabinofuranosylcytosine (ara-C), and the frequencies and types of chromosomal aberrations were scored in samples of c-metaphase cells collected at consecutive intervals throughout and following the cell cycle, under conditions which prevented cells in their second division following treatment from being included in the samples scored. For cells exposed in G2, both chromatid-type and chromosome-type lesions were observed. A chase with deoxycytidine (CdR) reduced the frequency of these lesions. There was some evidence that the initial lesions were gaps that may later have been converted into true chromosomal breaks. Lesions were produced chiefly at one chromosome location in early G2 and late S cells; the location was not specifically late-replicating. In all samples of cells in S at the time of exposure to ara-C, aberrations were chiefly, but not entirely, of the chromatid type; there was some evidence that their frequency was correlated with the ratio of DNA synthesis in the affected cells at the time of exposure to the drug. G1 cells were not susceptible to damage of ara-C. The level of damage in S cells was not affected by CdR chase. At no stage in the cell cycle did the lesions observed with ara-C imitate those produced by x-rays. (18 Refs)

54. ACTIVATION OF CYCLOPHOSPHAMIDE USING PERFUSED RAT LIVER SYSTEM AND INDUCTION OF SISTER CHROMATID EXCHANGES IN VITRO.

Abe T, Ide T, Tosa M, Takahashi T, Takino T
Dept. Medicine, Kyoto Prefectural Univ. Medicine, Kamigyoku 602 Kyoto, Japan
Hum Genet; 58(3):349 1981

The activation of cyclophosphamide (CPM) using perfused rat liver was studied in a simplified in vitro test system for the induction of sister chromatid exchanges (SCEs). The output fluid of CPM, perfused and recirculated in the liver of male Wistar rats, consisted of the CPM alkylating intermediate (AICPM). AICPM yielded an av 48.40 SCEs in human lymphocytes at concentrations of 10(-4) M. A clear dose relation was found between 10(-4) and 10(-6) M AICPM. (9 Refs)

55. EVALUATION OF EXPERIMENTAL PARAMETERS IN AN S9/HUMAN LEUKOCYTE SCE TEST WITH CYCLOPHOSPHAMIDE.

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Mutat Res; 85(5):347-356 1981

The effect of various cyclophosphamide (CP) concentrations on sister chromatid exchange (SCE) frequency and cell proliferation, and the influence of experimental parameters (S9 concentration, concentration of cofactors, and exposure time) on

CP-induced effects were examined in a human WBC test. The S9 fraction was prepared from livers of Aroclor-induced male rats. S9 mix alone did not influence SCE frequency or cell proliferation. CP, 1.7 x 10(-6) to 5.0 x 10(-5) M, produced increasing delay in cell proliferation. CP-induced SCE frequencies were strongly dependent on actual S9 concentration; cell proliferation was delayed with increasing S9 concentration. Studies with different concentrations of the cofactors (NADP and glucose-6-phosphatase in a ratio of 1:2) indicated an influence on the activity of S9 mix which was not as important as S9 concentration. SCE frequency increased, but cell proliferation was slightly inhibited with prolonged exposure times. CP at 1.7 x 10(-5) M was toxic in exposures greater than 2 hr. The importance of varying experimental parameters to avoid false-negative results in microsome tests is discussed. (28 Refs)

56. CYTOGENETIC STUDIES IN PATIENTS TREATED WITH ORAL RETINOID RO 10-9359.

Happle R
Universitats-Hautklinik, Von-Esmarch-Strasse 56, D-4400 Munster, W. Germany
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

Scoring for chromosome breakage (gaps, chromatid or isochromatid breaks, acentric fragments, and structural rearrangements) was carried out on 792 metaphase cells from patients treated with Ro 10-9359 and 658 metaphases from control individuals. Both the frequency of cells with aberrations and the frequency of aberrant metaphases in different individuals were essentially the same in the treated and control groups, indicating that Ro 10-9359, given po in therapeutic doses, does not induce chromosome breakage in man. (10 Refs)

57. CHROMOSOMAL ANALYSIS IN PATIENTS TREATED WITH THE AROMATIC RETINOID RO 10-9359.

Obe G, Tsambaos D
Institut fur Allgemeine Genetik, Arnimallee 5-7, D-1000 Berlin 33, W. Germany
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

Eighteen patients with psoriasis (13), lichen planus (3) and Darier's disease (2) received Ro 10-9359 (25-75 mg/day) for 4-24 wk. Chromosome analysis of their peripheral lymphocytes showed no increase in chromosomal aberrations and sister chromatid exchanges due to drug treatment. (16 Refs)

58. CHROMOSOME CHANGES IN HUMAN LYMPHOCYTES AFTER SEPARATE AND COMBINED TREATMENT WITH DIVALENT SALTS OF LEAD, CADMIUM, AND ZINC.

Gasiorek K, Bauchinger M
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Environ Mutagen; 3(5):513-518 1981

Venous blood from a healthy male donor was exposed to lead acetate (Pb + +), cadmium acetate (Cd + +), and zinc acetate (Zn + +) for 3 hr at 37 C separately and in combinations of two and three metal salts, respectively. The lymphocytes were then washed, and two separate cultures were set up from the pellet of 0.5-ml whole blood in fresh medium, fetal calf serum, and phytohemagglutinin and incubated for 48 hr. Colcemid was present for the final 3 hr. All structural chromsome aberrations and gaps were recorded. After Zn + + and Pb + + treatment, no significant differences were seen for gaps as compared with controls. Gaps tended to increase with the highest tolerated concentration. Following Cd + + treatment, gaps showed a dose-dependent increase. Structural aberrations were exclusively open breaks of the chromatid type or acentric fragments. Zn + + and Pb + + treatment produced the same effect as controls, while a significant increase was demonstrated for the higher concentrations of Cd + +. The aberrations observed after combination treatments with metal salts were similar to those observed after single metal salt treatment, with only a few exceptions. These findings are discussed with respect to heavy metal metabolism in human lymphocytes. (15 Refs)

59. CHARACTERIZATION OF A RAT LYMPHOCYTE CULTURE SYSTEM FOR ASSESSING SISTER CHROMATID EXCHANGE AFTER IN VIVO EXPOSURE TO GENOTOXIC AGENTS.

Kligerman AD, Wilmer JL, Erexson GL
Chemical Industry Inst. Toxicology, P.O. Box 12137, Research Triangle Park, NC, 22709
Environ Mutagen; 3(5):531-543 1981

A simple lymphocyte culture system that can be used to study cytogenetic damage in rats after in vivo exposure to genotoxic agents was devised. Experiments were conducted on the effect of media type and washing blood with phosphate buffered saline on mitotic activity; the effects of fetal calf serum and phytohemagglutinin (PHA) concentration on mitotic activity; the effect of PHA concentration on mitotic activity, sister chromatid exchange (SCE) frequency, and cell cycle kinetics; analyses of blast transformation time and cell kinetics; analyses of cell cycle kinetics; effect of bromodeoxyuridine (BrdU) in SCE frequency, cell cycle kinetics, and mitotic activity; and the effects of in vivo exposure to ethyl methanesulfonate (EMS) on SCE frequency, cell cycle kinetics, and mitotic activity. The system uses a small vol of blood, a low BrdU concentration and minimal culture time to obtain relatively high mitotic indexes, adequate numbers of second division metaphases, and consistently low baseline SCE frequencies. The critical steps in the process are the washing of the blood before inoculation and the use of between 2.0 and 4.0 ug PHA/ml medium. EMS produced long-lived lesions in rat lymphocytes that could lead to SCE formation upon blast transformation and cell division. (34 Refs)

60. HIGH INCIDENCE OF SISTER CHROMATID EXCHANGES AND CHROMATID INTERCHANGES IN THE CONDITIONS OF LOWERED ACTIVITY OF POLY(ADP-RIBOSE) POLYMERASE.

Hori T
Div. Genetics, Natl. Inst. Radiological Sciences, 4-Anagawa, Chiba 260, Japan
Biochem Biophys Res Commun; 102(1):38-45 1981

The effect of reduced activity of poly(ADP-ribose)polymerase on chromosome stability was studied in cultured Chinese hamster ovary cells (CHO-K1). Incubation of CHO-K1 cells in a medium containing the poly(ADP-ribose)polymerase inhibitor m-aminobenzamide significantly increased the incidence of sister chromatid exchanges and nonsister chromatid interchanges. Absence of nicotinamide in the medium enhanced the effects. (24 Refs)

61. SODIUM BUTYRATE BLOCKS HELA CELLS PREFERENTIALLY IN EARLY G1 PHASE OF THE CELL CYCLE.

Xue S, Rao PN
Dept. Biology, Beijing Normal Univ., Beijing, People's Republic of China
J Cell Sci; 51:163-171 1981

The effects of sodium butyrate on the cell-cycle traverse of HeLa cells was re-examined using the kinetic and the premature chromosome condensation methods of cell-cycle analysis. The results of this study indicate that the sodium butyrate effects are dose-dependent and cell-cycle phase-specific. Cells in the early G1 period are the most sensitive to the inhibitory effects of the drug. When HeLa cells in exponential growth were exposed to a 5 mM concentration of butyrate for 48 hr, 67% of the cell population was preferentially arrested in the early G1 period as indicated by the condensed morphology of the premature ly condensed chromosomes (PCC). There was no accumulation of cells in the G2 period. The results of this study suggest that hyperacetylation of histones induced by sodium butyrate does not necessarily result in decondensation of chromatin and the butyrate-enhanced protein, which has been reported to be present in butyrate-treated cells, may have a role in the regulation of the transition of cells from early G1 to the subsequent phases of the cell cycle. (Author abstract) (22 Refs)

62. CHEMICAL CARCINOGENESIS IN THE RAT: COMMON MODE OF ACTION OF CARCINOGENS AT THE CHROMOSOME LEVEL.

Sugiyama T, Ueda N, Maeda S, Shiraishi N, Goto-Mimura K, Murao S, Chattopadhyay SC
Dept. Pathology, Kobe Univ. Sch. Medicine, Chuo-ku, Kobe, Japan 650
JNCI; 67(4):831-839 1981

The chromosomal distribution of chromosome aberrations (CA) and sister chromatid exchanges (SCE) induced by various chemical carcinogens such as 7,12-dimethylbenz[a]anthracene, 7,8,12-trimethylbenz[a]anthracene, 1-butyl-1-nitrosourea, urethan, 4-nitroquinoline 1-oxide, 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, and the antineoplastic compound mitomycin C was studied with the use of noninbred Long-Evans male rat bone marrow cells in vivo and in vitro. The CA and SCE induced by these structurally different chemicals were distributed in similar pattern among and along chromosomes when the chemicals were given a short time (6 hr) before the metaphase cells were harvested. The specific distribution pattern of chemically induced CA and SCE along chromosomes was attributed to the late DNA replication of the vulnerable chromosome regions. Conversely, x-ray-induced CA were distributed more randomly. Thus the different chemical carcinogens were shown to exert a similar genetic effect at the chromosome level. (Author abstract) (38 Refs)

63. SOME EFFECTS OF TREATMENT OF HEN ERYTHROCYTES IN VITRO WITH N-METHYL-N-NITROSOUREA.

Ward TH, Itzhaki RF
Paterson Lab., Christie Hosp., Manchester M20 9BX, England
J Cell Sci; 51:153-162 1981

Studies have been made of the effect of N-methyl-N-nitrosourea on hen RBC in vitro. These were done to find whether the highly condensed state of the chromatin and the very low metabolic activity of these cells would affect the extent of methylation of the DNA and chromatin proteins and the persistence of any methylation sites in these macromolecules with time after treatment. Also, the effect of methylnitrosourea on incorporation of [3H]uridine into RNA has been examined. It has been found that the DNA, histones and non-histone proteins are methylated. The main methylation site in DNA is 7-methylguanine and its level is higher that that found by others in the DNA of other cell types after treatment with methylnitrosourea; however, methylation of the two types of protein (especially the histones) is re latively very low. The level of methylation decreases in the DNA and the chromatin proteins with time after treatment. The amount of [3H]uridine in RNA was found to decrease after the treatment. (Author abstract) (19 Refs)

64. CYTOGENETIC EVALUATION OF THE EFFECT OF HYPOXIA ON ANIMALS.

Bobkova NN
Inst. Medico-Biological Problems, Moscow, USSR
Genetika; 17(8):1493-1499 1981

Cytogenetic analysis of mice exposed to hypoxia showed significant increase of the mitotic activity and the frequency of poly- and hyperdiploid cells in the bone marrow on day 3 after exposure. Hypoxia caused slight decrease of the frequency of chromosome aberrations. (26 Refs) (In RUS)

GENERAL REVIEWS

65. CHROMOSOME ABERRATIONS AND THEIR RELEVANCE TO METAL CARCINOGENESIS.

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Environ Health Perspect; 40:173-180 1981

Current knowledge of the effects of metals on chromosomes is reviewed, and gaps in this knowledge and future research needs are discussed. The subjects covered include detection of somatic chromosome damage by analysis of metaphase chromosome aberrations (CAs), scoring for sister chromatid exchange, and scoring for micronuclei in maturing RBC; genetic effects of somatic CAs; chromosome changes in malignancies; correlations between CAs and immunologic impairment and aging; CAs in humans exposed to metal compounds (arsenic, cadmium, chromium, nickel, mercury, and lead): and the health implications of chromosome damage caused by metal exposure. A group of exposed persons with increased CA levels has a higher risk of developing cancer than a group with no increase in CAs. However, the quantitative risk estimate cannot be deduced from chromosome data for a single individual; on an individual basis, increased chromosome damage may also point to inherited susceptibility. (73 Refs)

66. EFFECTS OF METALS IN IN VITRO BIOASSAYS.

Sirover MA
Dept. Pharmacology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Environ Health Perspect; 40:163-172 1981

In vitro bioassays for detecting the mutagenicity and potential carcinogenicity of metal compounds are reviewed. Assays discussed include the Salmonella typhimurium and Escherichia coli assays that quantitate the ability of metals to revert the bacteria to histidine prototrophy and to tryptophan prototrophy, respectively, and the use of Bacillus subtilis strains deficient in DNA repair to determine growth inhibitory effects of metals. Other bioassays examine the ability of metals to induce thioguanine or azaguanine resistance in Chinese hamster cells, enhance viral transformation in hamster cells, transform Syrian hamster cells, and induce chromosome aberrations in hamster and rat cells and human lymp hocytes. Correlations between in vitro bioassays and in vivo carcinogenicity are discussed. (82 Refs)

67. SISTER CHROMATID EXCHANGE (SCE) AND STRUCTURAL CHROMOSOME ABERRATION IN MUTAGENICITY TESTING.

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Hum Genet; 58(3):235-254 1981

An objective analysis is presented of data gained so far relative to the value in mutagenicity testing of sister chromatid exchange (SCE) and classical chromosome aberration (CA) analysis. Detailed studies are reported on spontaneous SCE and chromosome damage in normal cells, and in cells of patients with genetic and neoplastic disease. Qualitative results on SCE induction and CA are presented relative to radiation, chemicals, chromosomal breakage syndromes and virus. Quantitative results are presented on potent inducers of SCE and break aberrations, substances inducing SCE but not breaks in the same test system, and clastogens with no or minor SCE-inducing activity. A section deals with modification of SCE and chromosome breakage: clastogens and anticlastogens. A discussion of molecular aspects of SCE induction and breakage involves consideration of evidence for the primary lesions leading to SCE formation, role of replication and involvement of repair mechanisms. These studies indicate SCE and structural CA are two largely different cytogenetic endpoints of mutagenic action. It is suggested that the SCE-technique is a valuable additional method for cytogenetic testing, which, however, is not adequate to replace the classical methods of analysis of structural chromosome damage. (165 Refs)

68. CLASSIFICATION OF ACUTE LEUKEMIAS.

Imbert M, D'Agay MF, Andre C, Sultan C
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Ann Biol Clin (Paris); 39(4):155-164 1981

Morphological, electron microscopic, immunologic, and chromosomal classifications of acute leukemias are discussed. Morphological classification is based on blood and bone marrow smears and on certain simple cytochemical reactions. According to this schema leukemia can be classified as acute lymphoblastic (L1, L2, or L3, Burkitt's type) and acute myeloblastic (without or with maturation, hypergranular promyelocytic, myelomonocytic, acute monocytic, and erythroleukemia, M1-6, respectively). Electron microscopic analysis permits the analysis of the fine structure of Auer bodies and allows the recognition of the myeloid (myeloblastic or megakaryocytic) nature of certain leukemias classified as lymphoblastic or undifferentiated on the basis of cytological or cytochemical findings. Immunologic study, using membrane markers, provides useful information for the classification of lymphoblastic leukemias as T-cell, B-cell, and non-T, non-B-cell leukemias. Biochemical tests utilizing lysozyme and terminal-deoxynucleotidyltransferase measurements are described. Karyotypic anomalies can also be associated with various forms of acute lymphoblastic or myeloblastic leukemia. (57 Refs) (In FRE)

69. MECHANISMS OF TOLERANCE TO DNA LESIONS IN MAMMALIAN CELLS.

Meneghini R, Menck CF, Schumacher RI
Dept. Biochemistry, Inst. Chemistry, Univ. Sao Paulo, C.P. 20780, Sao Paulo, Brazil
Q Rev Biophys; 14(3):381-432 1981

The way in which mammalian cells deal with a large burden of unexcised DNA lesions is discussed. The biological consequences of unexcised DNA lesions are considered in terms of cell killing, cell mutation, cell transformation, enhanced virus reactivation, and sister chromatid exchanges. These different biological effects seem to be triggered during DNA replication. Thus, the damaged template has to be replicated in order for the chain of events leading to a certain effect to be initiated. DNA replication on a damaged template is discussed in relation to information from bacterial systems, DNA containing lesions replicated in mammalian cells, effect of template-strand lesions on the rate of DNA synthesis and the structure of the daughter strand, inhibition of replication fork by lesions in the template strand, DNA synthesis along the lesions (postreplication repair), and mechanisms of postreplication repair (recombination, branch migration, 'translesion synthesis', and relief of blocked sites by joining of adjacent replicons). Hints of the inducibility of tolerance to DNA lesions come from distinct approaches such as the enhancement of DNA chain elongation, recovery of the rate of DNA synthesis, recovery in survival, enhanced virus reactivation, and induction of proteins by DNA-damaging agents. (163 Refs)

70. IN VITRO MODELS AND METHODS FOR BIOASSAY AND STUDIES OF CELLULAR MECHANISMS.

Belman S, Casto B, Flessel CP, Lane BP, Loeb L, Rossman T, Sirover MA, Vainio H, Whiting R, Zakour R
New York Univ. Medical Center, New York, NY, 10016
Environ Health Perspect; 40:35-42 1981

The use of in vitro systems to detect metal carcinogens and study the mechanisms of carcinogenesis is discussed. These systems include mutagenesis in bacterial and mammalian cells, in vitro transformation, cell-free systems, chromosome aberrations, sister chromatid exchanges, and micronucleus tests. Chromium carcinogenesis is described as an example. General conclusions and recommendations for the future are presented. (56 Refs)

71. MYELOPROLIFERATIVE DISORDERS: III CML: FURTHER STUDIES ON THE ROLE OF CYTOGENETICS IN DIAGNOSIS, PROGNOSIS AND MANAGEMENT.

Fuscaldo KE, Brodsky I, Kahn SB, Conroy JF, Marfurt K
Herbert L. Orlowitz Cancer Inst., 230 North Broad St., Philadelphia, PA, 19102
Haematologica (Pavia); 66(4):461-488 1981

The use of periodic cytogenetic monitoring of patients with chronic myelocytic leukemia is discussed in relation to the establishment of diagnosis and the assessment of prognosis. Data are presented suggesting that sequential cytogenetic studies performed during the course of a patient's disease may indicate impending transformation of the chronic disease state or remission or relapse of the acute phase. (113 Refs)

72. THE RELATIVE ROLE OF VIRAL TRANSFORMATION AND SPECIFIC CYTOGENETIC CHANGES IN THE DEVELOPMENT OF MURINE AND HUMAN LYMPHOMAS.

Klein G
Dept. Tumor Biology, Karolinska Institutet, 104 Stockholm 60, Sweden
Haematol Blood Transfus; 26:3-10 1981

Lymphoma and leukemia development in mice and men, where there is extensive evidence for the role of the specific genetic changes recognizable at the chromosome level, is discussed. Topics considered include human lymphomas, murine T cell leukemia, the relationship of trisomy to murine T-cell leukemia, and the role Abelson virus as a transducer or cellular gene. Various conclusion were drawn: transformation in vitro is not synonymous with tumorigenicity in vivo; host cell controls can modify the expression of transformation in vivo; and host cell controls can reverse tumorigenic to nontumorigenic phenotypes. The concept of convergence is discussed in relation to tumor evolution. According to this concept viruses play essentially the role of initiators in tumor progression, specific genetic changes are responsible for the transition of preneoplastic to frankly malignant cells, and the cytogenetic changes act by shifting the balance between genes that favor progressive growth in vivo and genes that counteract it. (85 Refs)

73. CHROMOSOME STUDIES IN CHILDREN AND ADULTS WITH LEUKEMIA.

Rowley JD
Dept. Medicine, Section Hematology/Oncology, Box 420, 950 East 59th St., Chicago, IL
Haematol Blood Transfus; 26:27-33 1981

Chromosome abnormalities are described in various myeloid leukemias including Philadelphia chromosome (Ph1)-positive myelogenous leukemia (chronic and acute), acute nonlymphocytic leukemia, and acute lymphoblastic leukemia. Within each category, the data that have been collected are correlated with clinical information. The identification of nonrandom chromosome changes in these various myeloproliferative and lymphoproliferative disorders are reviewed. Although the data available for these disorders are quite variable both with regard to the number of patients studied and the quality of banding, patterns of chromosome changes can be discerned that differ among the various groups. Wherever possible these pattern were related to structural and functional characteristics of these cells as determined by others as well as to the clinical correlations of particular chromosome changes. (26 Refs)

74. THE IMPLICATIONS OF NONRANDOM CHROMOSOME CHANGES FOR MALIGNANT TRANSFORMATION.

Rowley JD
Dept. Medicine, Section Hematology/Oncology,, Box 420, 950 East 59th St., Chicago, IL, 60637
Haematol Blood Transfus; 26:151-155 1981

How and why chromosome changes occur are discussed in relation to malignant transformation. The mechanism for the production of specific, consistent, reciprocal translocations is unknown. A clear difference in preferential break points for chromosome translocations, was observed depending on whether the rearrangement resulted in a balanced or an unbalanced aberration. Other possible explanations depend on either chromosomal proximity, since translocations may occur more frequently when two chromosomes are close together, or regions of homologous DNA that might pair preferentially and then be involved in rearrangements. Kinds of gene loci that can provide a proliferative advantage during nonrandom changes are considered including the host genome and chromosome changes related to gene dosage (homogeneously staining regions and double minute chromosomes and evidence for gene amplification). (28 Refs)

75. THE DIFFERENT ORIGIN OF PRIMARY AND SECONDARY CHROMOSOME ABERRATIONS IN CANCER.

Levan G, Mitelman F
Genetiska Institutonen, Goteborgs Universitet, Stigbergsliden 14, 41463 Goteborg, Sweden
Haematol Blood Transfus; 26:160-166 1981

Based upon an analysis of chromosome aberrations in 1,827 cases of human malignancy, a hypothesis (model) is presented to explain the role of chromosome aberrations in the development of malignancy. Primary, active chromosome changes are attributed to the direct interaction between the oncogenic agent and the host cell's genome; these changes are mainly somatic mutations, but may be associated with structural changes visible in the microscope. Secondary, passive changes are believed to arise randomly by nondisjunction and structural rearrangements and to be followed by selection of cells with changes that amplify primary changes so that they appear as nonrandom chromosome patterns. The neoplasms in the 1,827 cases fell into three large categories: myeloproliferative disorders, lymphoproliferative disorders, and solid tumors; these three groups were further subdivided into 15 tumor types. Chromosome aberrations were identified by banding techniques; it was found that specific aberrations clustered selectively on specific chromosomes in each type of neoplasm. (8 Refs)

76. REGIONAL GENE MAPPING OF HUMAN CHROMOSOMES PURIFIED BY FLOW SORTING.

Carrano AV, Lebo RV, Yu LC, Kan YW
Biomedical Div., Lawrence Livermore Lab., L-452, Livermore, CA, 94550
Haematol Blood Transfus; 26:156-159 1981

The use of analysis and sorting of chromosomes using fluorescence-based high speed flow systems for regional gene mapping of human chromosomes is described. The methodology for this analysis and sorting procedure is described. There are three requirements for regional gene mapping: the ability to resolve the chromosome of interest in the flow distribution, a DNA probe specific for the gene to be mapped, and cell strains possessing rearrangements of the chromosome to be mapped. The regional mapping of the human beta, gamma, and delta-globin genes was used to illustrate the principles involved. It was suggested that chromosomes purified by flow sorting have potential application to gene transfer and to the molecular biology of chromosome structure and function. It should be possible to examine DNA or protein unique to a single chromosome and, for example, to examine the DNA associated with specific chromosomal alterations in hematological disorders such as translocation between chromosomes 9 and 22 in chronic myelogenous leukemia. (18 Refs)

77. SOME RECENT TRENDS IN STUDIES OF HUMAN LYMPHOID CELLS: B-CELLS, EPSTEIN-BARR VIRUS, AND TRANSFORMATION.

Zeuthen J, Kle[illegible] G

Institute for Human Genetics, Bartholin Byggningen, Aarhus Univ., 8000 Aarhus C, Denmark

Haematol Blood Transfus; 26:179-190 1981

A review of recent findings in work on regulatory mechanisms involved in the selective expression of differentiated markers in human B-cell lines and the types of controls involved in the expression and function of Epstein-Barr virus (EBV)-associated markers in human cells, with special attention to the relationship between the expression of EBV functions and the expression of transformation. Because EBV is a lymphotropic virus in man, infection of lymphoid cell lines is reviewed. Chromosome studies on lymphoblastoid cell lines and B-cell lines of BL origin with regard to ploidy and karyotype abnormalities following EBV infection are discussed in detail. Studies of the immunoglobulins synthesized and the major histocompatibility antigens expressed by hybrid lymphocytes are presented. The expression of EBV, the EBV-determined nuclear antigen, and cell transformation by EBV are thoroughly reviewed. (79 Refs)

78. BACTERIAL SYSTEMS FOR CARCINOGENICITY TESTING.

Mohn GR

Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands

Mutat Res; 87(2):191-210 1981

The development of bacterial genetic tests and their potential value for qualitative detection and quantitative potency ranking purposes are reviewed. The development of bacterial test systems is described. The most widely accepted bacterial test system possesses a combination of induced histidine auxotrophs of Salmonella in a plate assay. Most systematic comparative studies on carcinogenesis and mutagenesis have been performed in the Ames plate assay with the strains designated TA1535, TA1537, TA 1538, TA98, and TA100. The qualitative correlation between mutagenicity and carcinogenicity is considered. Some chemicals are active in several different bacterial systems while others are mutagenic only in one or a few specific systems. Examples of tumor incidence enhancing chemicals in experimental animals and/or humans with no detectable or inconclusive mutagenic activity in bacterial systems and some bacterial mutagens with no evidence for or no sufficient data on animal carcinogenicity are described. Bacterial mutagenicity tests may be useful in predicting tumor-initiating potency in three instances: direct extrapolation from in vitro bacterial data obtained by standard procedures, indirect extrapolation from in vitro bacterial data obtained with representative genetic endpoints and backgrounds on the basis of correction according to extrapolation factors determined from quantitative comparative mutagenicity studies in prokaryotic and eukaryotic model organisms, and extrapolations from host-mediated assays performed with indicator microorganisms present in target organs of animals treated at practical exposure concentrations. Future prospects for bacterial test systems in mutagenicity and carcinogenicity testing are described. (153 Refs)

79. MUTAGENESIS BY CHEMICAL AGENTS IN V79 CHINESE HAMSTER CELLS: A REVIEW AND ANALYSIS OF THE LITERATURE.

Bradley MO, Bhuyan B, Francis MC, Langenbach R, Peterson A, Huberman E

Merck Inst. for Therapeutic Res., West Point, PA, 19486

Mutat Res; 87(2):81-142 1981

The current literature on chemically induced specific locus mutations in the V79 Chinese hamster cell line are reviewed and evaluated. Characteristics of V79 cells, various genetic markers, and protocols for mutant induction by chemicals in the presence and absence of activation systems are described. The chemicals which were tested in V79 cells for mutagenic activity are listed. The usefulness of V79 cells for the screening of environmental chemicals which may be hazardous to humans is evaluated. Mutagenesis assays are discussed in relation to characteristics of the V79 cell line, genetic markers (hypoxanthine-guanine phosphoribosyl transferase [HGPRT] locus, reversion of HGPRT- mutants, ouabain-resistance, drug resistance, and auxotrophic, prototrophic and temperature-sensitive mutants) of V79 cells, and suggested and testing (toxicity and dose selection, standard mutagen treatment conditions, expression time, mutant selection, identification of phenotypic variants as presumptive genotypic variants, metabolic activation, cell-mediated mutagenesis, tissue homogenate-mediated mutagenesis, positive and negative controls, experimental design) protocols. Test performance is evaluated based on an analysis of the literature. The strengths and weaknesses of the V79 assay are considered. The role of the assay in mutagenicity and carcinogenicity testing programs is discussed. (162 Refs)

80. MAMMALIAN IN VIVO AND IN VITRO CYTOGENETIC ASAYS: A REPORT OF THE U.S. EPA'S GENE-TOX PROGRAM.

Preston RJ, Au W, Bender MA, Brewen JG, Carrano AV, Heddle JA, McFee AF, Wolff S, Wassom JS

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Mutat Res; 87(2):143-188 1981

An assessment made by the United States Environmental Protection Agency Gene-Tox Program's Work Group on Mammalian cytogenetics of the clastogenic effects of chemicals in in vivo and in vitro mammalian assays based on 177 papers is presented. General considerations used in the interpretation of data included differential sensitivity of cells in different stages of the cell cycle, metabolic activation, suitability of protocols, and tabular presentation of data base. The protocols for testing and the chemicals reviewed for the bone marrow, spermatogonia, spermatocyte (treated spermatogonial stem cells and treated spermatocytes), oocytes and early embryo, in vitro cell culture assay, and peripheral leukocyte or lymphocyte assays are presented. Advantages and disadvantages of the cytogenetic assay systems are considered. (162 Refs)

OTHER RELATED STUDIES

81. SUCCESSIVE GENERATIONS OF MICE PRODUCED FROM AN ESTABLISHED CULTURE LINE OF EUPLOID TERATOCARCINOMA CELLS.

Stewart TA, Mintz B
(c/o Mintz) Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA, 19111
Proc Natl Acad Sci USA; 78(10):6314-6318 1981

The possibility of utilizing mouse teratocarcinoma stem cells as intermediaries for production of new strains of mice with preselected mutant or foreign genes requires that, after propagation in culture (to allow for genetic manipulation and selection), the cells be capable of normalization and orderly development in carrier embryos and, ultimately, of germ-cell formation. Heretofore, no in vitro cell line has fulfilled all these requirements. A karyotypically normal teratocarcinoma culture line was recently established in this laboratory and now has been investigated as a candidate. The line, designated METT-1, is chromosomally female (X/X) and was obtained from the 129 (agouti-colored) inbred strain. The developmental potential of these cells was tested, after prolonged culture and freezing and thawing, by microinjecting them into early (blastocyst stage) embryos of the C57BL/6 (black) strain. Among 312 experimental animals examined at 1 wk of age, there were 41 mice (21 females and 20 males) that displayed the coat colors of both strains. This frequency (13%), as well as the extent of the coat areas derived from the cell line, greatly surpasses the contributions observed in all previous experiments, whether with other in vitro teratocarcinoma cell lines or with in vivo transplant lines. The developmental totipotency of METT-1 cells became evident from the presence of substantial amounts of 129-strain cells (bearing an isozyme marker) in all internal tissues of an individual whose coat was largely agouti. The culture-cell lineage also proved to be capable of giving rise to reproductively functional oocytes. Of nine mosaic-coat females test-mated to C57BL/6 males, one produced progeny of the diagnostic agouti color in two litters; these heterozygous F1 offspring in turn transmitted their marker genes to F2 homozygous segregants. Thus, the METT-1 teratocarcinoma line bridges the gap between in vitro cell propagation and in vivo development and between the soma and the germ line. This creates the option of producing new mouse strains with predetermined genetic changes designed as probes of developmental regulation or as models of human genetic diseases. (Author abstract) (28 Refs)

82. IMPLICATIONS OF NEW HIROSHIMA AND NAGASAKI DOSE ESTIMATES: CANCER RISKS AND NEUTRON RBE.

Straume T, Dobson RL
Hazards Control Dept., Lawrence Livermore Natl. Lab., PO Box 808, Livermore, CA, 94550
Health Phys; 41(4):666-671 1981

Dose-response relations for radiation-induced leukemia, breast cancer, total malignancies, and chromosome aberrations in atomic bomb survivors were analyzed with the use of new dose estimates that differ substantially from the generally accepted values. They indicate that the gamma ray component and total dose were higher in Hiroshima than previously believed and lower in Nagasaki; neutron components were lower in both cities. Dose-response curves for leukemia and breast cancer were similar in the two cities, but those for total malignancies and chromosome aberrations demonstrated significant inter-city differences. The inter-city differences were due to an increase in neutron relative biological effectiveness (RBE) with decreasing dose due to diminished gamma-ray effectiveness. The neutron RBE for leukemia and breast cancer induction remain to be clarified. (13 Refs)

83. CLINICAL UTILITY OF LEUKEMIA CELL TERMINAL TRANSFERASE MEASUREMENTS.

McCaffrey R, Lillquist A, Sallan S, Cohen E, Osband M

Section Medical Oncology, Evans Dept. Clinical Res., Univ. Hosp., Boston, MA

Cancer Res; 41(11,part2):4814-4820 1981

Interest in the DNA-synthetic enzyme terminal deoxynucleotidyl transferase (TdT) has developed from two sets of observations: first, in normal animals, it occurs only in immature thymic lymphocytes and in a subpopulation of bone marrow lymphocytes; second, it is present in the blast cells of almost of all patients with acute lymphoblastic leukemia. A prospective trial to evaluate blast cell TdT as a predictor of responsiveness to vincristine and prednisone in 30 Philadelphia chromosome-positive patients with blastic chronic myelogenous leukemia was undertaken. Eleven of 16 TdT-positive patients responded, whereas only 1 of 14 TdT-negative patients showed improvement. Among TdT-positive patients under the age of 50 yr, the response rate was 78%. Enzyme-negative patients under the age of 50 had an 11% response rate. Blast cell morphology (ie, lymphoblastic vs myeloblastic) had no significant correlation with either responsiveness or TdT activity. These results suggest that blast cell TdT activity may identify leukemic patients who are likely to respond to vincristine and prednisone irrespective of their conventional classification. (Author abstract) (49 Refs)

84. BLEOMYCIN INDUCED INHIBITION OF DNA SYNTHESIS IN ATAXIA-TELANGIECTASIA CELL LINES.

Edwards MJ, Taylor AM, Flude EJ

Cancer Res. Campaign Lab., Dept. Cancer Studies, Medical Sch., Univ. Birmingham, Birmingham B15 2TJ, England

Biochem Biophys Res Commun; 102(2):610-616 1981

Inhibition of DNA synthesis by bleomycin (30-300 ug/ml) was studied in fibroblast and lymphoblastoid cells from normal individuals and lymphoblastoid cells from ataxia-telangiectasia (AT) patients. DNA synthesis was measured by incorporation of [14C]thymidine. In normal cells bleomycin produced a biphasic inhibition of DNA synthesis which increased sharply with bleomycin dose at low dose levels and leveled off at higher doses. The first, sharp increase in inhibition may be due to inhibition of replicon initiation, and the second, more shallow component may result from inhibition of chain elongation. Inhibition of DNA synthesis was much slower in cells from AT patients than in normal cells at bleomycin doses less than 100 ug/ml. Low and high mol wt DNA fractions were not altered in AT cells. Replicon initiation and chain elongation were inhibited only at bleomycin doses of 100 ug/ml or more. Results suggest a defect in repair of bleomycin-caused damage in AT cells. (24 Refs)

85. INDUCTION OF GENE MUTATION IN AND CELL TRANSFORMATION OF MAMMALIAN CELLS BY MODIFIED PURINES: 2-AMINOPURINE AND 6-N-HYDROXYLAMINOPURINE.

Barrett JC
Environmental Carcinogenesis Group, Lab. Pulmonary Function, and Toxicology Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC, 27709

Proc Natl Acad Sci USA; 78(9,part2):5685-5689 1981

A classical mutagen in prokaryotic systems, 2-Aminopurine is inactive as a carcinogen in two animal species. To determine the basis for this discrepancy in the correlation between carcinogenesis and mutagenesis, the ability of 2-aminopurine to induce somatic mutation and neoplastic transformation concomitantly in the same cellular system was examined. 6-N-hydroxylaminopurine, a related modified purine that is a mutagen and a carcinogen, was also studied. 2-Aminopurine was a mutagen in Syrian hamster embryo cells, but its activity was very weak. The max induced mutation frequency with either of two mutational markers was only 7 x 10(-6) mutants per surviving cell. 2-Aminopurine also induced morphological transformation of the cells under the same conditions, but the frequency was only approx 0.04% per surviving colony. Neoplastic transformation of the cells after 2-aminopurine treatment was not observed in these experiments. These results indicate that 2-aminopurine is, at best, a weak transforming agent. The lack of carcinogenic activity in vivo with 2-aminopurine is consistent with these observations. In contrast to the results with 2-aminopurine, 6-N-hydroxylaminopurine was very effective mutagen in these cells (up to 10(-3) mutants per survivor) and induced morphological transformation of the cells in a dose-dependent manner. Furthermore, neoplastic transformation was induced by this nucleic acid base analog, the correlation of mutagenic activity with transforming ability of these two modified purines supports a relationship between mutagenesis and carcinogenesis. However, relative to other carcinogens, there is a quantitative difference in the ability of 6-N-hydroxylaminopurine to induce cell transformation and mutation. For example, in benzo[a]pyrene-treated cultures, the ratio of the frequency of induced morphological transformation to that of somatic mutation was approx 100, whereas for 6-N-hydroxylaminopurine-treated cultures, the ratio of transformation to mutation was only 3-12.5. This indicates that 6-N-hydroxylaminopurine is less potent than benzo[a]pyrene in inducing transformation when compared at equal mutagenic potency. This is consistent with our hypothesis that cell transformation, and possibly cancer, occurs predominantly as the result of a mutation at the chromosome level rather than a gene mutation. (Author abstract) (27 Refs)

86. INDUCTION OF TUMOR RESISTANCE BY HYBRID CELL LINES BETWEEN HUMAN ACUTE LYMPHOCYTIC LEUKEMIA CELLS AND MOUSE MYELOMA CELLS.

Isobe K, Kawashima K, Watanabe E, Yamada K, Nagai Y, Nakashima I

First Dept. Internal Medicine, Sch. Medicine, Nagoya Univ., 65 Tsurumai-cho, Schowa-ku, Nagoya 466, Japan

Gan; 72(5):705-712 1981

Three hybrid cell lines were derived from the fusion of BALB/c mouse NS-1 myeloma cells and human acute lymphocytic leukemia cells. Hybrid clones contained almost all of the mouse chromosomes and a few human chromosomes, and induced tumors in BALB/c and BALB/c nu/nu mice when inoculated sc. However, the tumors of BALB/c mice subsided spontaneously within 1 mo. The mice which survived the inoculation of 5 to approx 10 x 10(6) hybrid cells were able to reject a subsequent challenge with 5 x 10(6) NS-1 cells. Spleen cells or lymph node cells from immune mice were injected into BALB/c mice. These mice lived longer than the mice which received normal spleen cells or normal lymph node cells, when challenged with 5 x 10(6) NS-1 cells. These results suggest that a rearrangement of tumor-specific antigens on human/mouse hybrid cells can induce immunogenicity. (Author abstract) (20 Refs)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

CLINICAL STUDIES OF CHROMOSOMES IN HUMAN CANCER

1. CYTOGENETIC STUDY OF MALIGNANT AND BENIGN EFFUSIONS.

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Neoplasma; 28(4):463-471 1981

The direct chromosome study of mitotic cells in effusions was performed in 49 patients with malignant and 5 with benign effusions. Cytogenetic analysis correctly identified 69.3% of malignant effusions, standard cytology 79.6%. With both methods combined 95.9% of all cases were correctly diagnosed as malignant. The presence of mitoses in the effusions was found to be an unfavorable prognostic sign and was correlated with a shorter survival. Chromosome analysis of the malignant effusions revealed stemlines with extensive numerical and structural rearrangements. No consistent marker chromosome was detected in the histologically similar tumor types. Normal chromosomes number 1 and 14 were preferentially lost from the karyotype of malignant cells. In two samples double min were observed. (Author abstract) (25 Refs)

2. CLONAL ORIGIN OF LEUKEMIA: SITE OF ORIGIN IN THE STEM CELL HIERARCHY AND THE SIGNIFICANCE OF CHROMOSOMAL CHANGES.

Boggs DR, Lajtha L, Brecher G, Bernard J, Gallo R, Bessis M, Greaves MJ, Van Beddum DW, McCulloch EA
Dept. Medicine, Univ. Pittsburgh, Sch. Medicine, Pittsburgh, PA, 15261
Blood Cells; 7(2):205-215 1981

The strongest evidence that hematologic neoplasms are clonal is derived from analysis of cells in patients heterozygous for A and B isozymes of glucose-6-phosphate dehydrogenase. Clonality of chronic lymphoid leukemia is also suggested by studies of surface immunoglobulin of cells of most patients. Clinical and other data are presented as to possible site of origin of cancer in the hematopoietic stem cell hierarchy. Data are presented which suggest that chromosome abnormalities and morphologic abnormalities are not necessarily present uniformly throughout the clone. Thus, normal appearing, chromosomally normal cells may be part of the clone in acute and chronic myeloid leukemia; in some patients both abnormalities may exist as independent variables. If it should be proven the chromosome abnormality is only a subpopulation of the leukemic clone, then that abnormality cannot be considered the cause of leukemia. However, the abnormality could still represent an epiphenomenon of genetic damage in that chromosome or another chromosome, which was responsible for leukemic development and which also was expressed by visible chromosomal abnormalities in certain cells. (10 Refs)

3. CHROMOSOMAL ABERRATIONS IN LYMPHOPROLIFERATIVE DISEASES.

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Medicina (B Aires); 41(3):297-300 1981

The 25 patients studied were diagnosed as: 8 non-specific lymphadenitis, 2 giant follicular hyperplasia, 5 Hodgkin's disease, and 10 non-Hodgkin's lymphoma. The lymphadenitis patients (5 women and 3 men) had normal karyotypes: 40, XX and 46, XY respectively, they were the control group. The two cases of giant follicular hyperplasia had non specific number anomalies affecting different chromosomal groups. The five Hodgkin's disease patients, all had number anomalies, two were specific clones: one with 1 5q+ marker and one with complete 21 trisomy. Of the 10 non-Hodgkin's lymphomas: 7 were little differentiated diffuse lymphocyte lymphomas, and 3 well differentiated nodular lymphocyte lymphomas, all with important chromosomal anomalies. Half of them had numerical or structural anomalies of chromosome 1, which caused partial or total trisomies in the long part of that chromosome, recurrent markers were 1q+, 1p+, ans 1+. Of the other patients two had 14q+ marker, one had 6q- marker, two were clones with one and two chromosomes respectively in a ring. (16 Refs) (In SPA)

4. CYTOGENETICS IN THE ACUTE LEUKEMIAS.

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Sangre (Barc); 26(5B):738-755 1981

Out of 64 cases of acute leukemia (47 non-lymphoblastic and 17 lymphoblastic ones) in which cytogenetic studies were performed, 30 had normal karyotype (22 non-lymphoblastic and 8 lymphoblastic). The acute non-lymphoblastic leukemias with normal karyotype had a mean survival close to 11 mo, as opposed to 2-1/2 mo for the cases in which all the leukemia cells had abnormal karyotypes. The nine patients with WBC count above 100,000/cu mm had survivals slightly over 4 mo in spite of the normal karyotype found in seven of them. Chromosome 8 trisomy was the commonest numeric alteration, and it was seen in both leukemia groups; t(8q-; 21q+) associated to loss of the Y chromosome was found in a patient with M2 non-lymphoblastic leukemia, and this represents a 2% frequency in the series. Two patients with L3 lymphoblastic leukemia showed the same structural alteration, t(8q-; 14q+); one of them had other cytogenetic anomalies including two acrocentric marker chromosomes comprised of genetic material from chromosome (1(q21 q44)) translocated into a Y gonosome. The similarity of both cases with those of Burkitt lymphoma from a clinical, cytological, and cytogenetic standpoint is further evidence in support of the identity of L3 lymphoblastic leukemia and Burkitt lymphoma, which could be regarded as different manifestations of a unique disease status. (Author abstract) (58 Refs) (In SPA)

5. THE 5Q- CHROMOSOME IN PRELEUKAEMIA AND ACUTE LEUKAEMIA.

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Scand J Haematol; 27(2):119-129 1981

Thirteen patients with the 5q- chromosome are described. In six patients the 5q- chromosome was the sole aberration. Ten patients had preleukemia, 1 a preleukemia-like syndrome after treatment of polycythemia vera, a 2 acute myeloid leukemia. The prognosis was especially poor in terms of survival in preleukemic patients with three or more affected chromosomes: none of these six patients survived for more than 6 mo. In four patients the hematological picture resembled 'the 5q- syndrome'. In the long arm of chromosome No. 5 deletions of three different kinds were detected. They were named according to the size of the 5q- marker: the short type (10 patients), the intermediate type (1 patient) and the long type (2 patients). There was no clear correlation between the clinical picture and the type of deletion. While the break points cannot always be exactly defined, our data and those reviewed from the literature suggest that the loss of a segment of regions 5q2 or 5q3 is common to all or most deletions. (Author abstract) (33 Refs)

6. TERMINAL TRANSFERASE EXPRESSION IN RELAPSED ACUTE MYELOID LEUKAEMIA.

Bradstock KF, Pizzolo G, Papageorgiou ES, Cetto GL, Prentice HG, Ganeshaguru K, Prentice AG, Smith A, Chilosi M, Ambrosetti A, Hoffbrand AV
(c/o Hoffbrand) Dept. Haematology, Royal Free Hosp., Hampstead, London NW3 2QG, England
Br J Haematol; 49(4):621-627 1981

In three cases of acute myeloid leukemia marked increases in expression of the nuclear enzyme, terminal deoxynucleotidyl transferase (TdT), were observed during disease relapse. The first case was heterogeneous at diagnosis, consisting of subpopulations of large TdT- myeloblasts and small TdT+ blasts; however, at relapse there was complete replacement by TdT+ lymphoblasts. The other cases at diagnosis were both typical acute myeloid leukemia, TdT-; at relapse, one showed a mixture of TdT- myeloblasts and TdT+ lymphoblasts, while in the other, TdT was demonstrated on a subpopulation of myeloblasts. No chromosomal abnormalities were found. It is suggested that in the first two cases these phenomena may have been due to leukemic involvement of a pluripotential stem cell, or that sub-clones with different properties may have coexisted. In the third case at relapse, TdT was expressed aberrantly by malignant myeloid cells. (Author abstract) (26 Refs)

7. COEXISTENCE OF MYELOID AND LYMPHOID NEOPLASTIC SUBPOPULATIONS IN CHRONIC MYELOGENOUS LEUKEMIA.

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Med Pediatr Oncol; 9(5):467-472 1981

Serial cytogenetic studies have been performed on a child with Philadelphia chromosome (Ph1)-positive chronic myelogenous leukemia (CML) and correlated with clinical, morphologic, and cytochemical data in an attempt to elucidate further the natural history of leukemic progression observed in this disease. Once the initial blast crisis had occurred, two genetically different leukemic clones of cells, one presumably having arisen from the other, coexisted throughout the remainder of the patient's course. The initial clone comprised differentiating myeloid cells, while the second clone appeared on morphologic and cytochemical grounds to be lymphoid and blastic. A dynamic equilibrium existed between these two populations of cells, with the balance altered by chemotherapy and/or other selective pressures. The leukemic progression demonstrated in this case is consistent with the concept of clonal evolution of malignant cell populations. In planning therapy, it may be necessary to consider each of these coexistent clones and their different therapeutic requirements. (Author abstract) (13 Refs)

8. CHROMOSOMAL ABNORMALITIES IN A CASE OF HAIRY CELL LEUKEMIA.

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Leuk Res; 5(4/5):431-435 1981

Chromosomal abnormalities found in a 76-yr-old male hairy cell leukemia patient are described. The patient was typical except for the production of kappa IgG paraprotein and had not received cytotoxic chemotherapy. Low dose prednisone was being administered. Considerable metaphases were obtained from phytohemagglutinin-stimulated culture. In 162 metaphases counted, the chromosome number varied from 43 to 48. Of a total of 29 metaphases karyotyped, 17 had 46 chromosomes, 11 of which were normal, 1 showed an additional chromosome 2 and a missing C group chromosome, 1 showed a translocation between chromosomes 1 and 14, t(1q-;14q+), and 4 metaphases showed a 46, XY, 3q+, 14q- karyotype. Trisomy 2 was found in four karyotyped metaphases with 47 chromosomes and in one spread of 48 chromosomes. An additional chromosome 2 was found in 17% of cells studied. The other clonal abnormality, seen in 14% of the cells analyzed, also involved a member of the A group chromosomes: a chromosome 3 showing additional material on the long arm (3q+), which may have been translocated from the long arm of chromosome 14, as all the spreads showing a 3q+ chromosome also showed a 14q- chromosome. The difficulty in obtaining metaphases in hairy cell leukemia and other B cell malignancies is discussed. (8 Refs)

9. A CLINICOPATHOLOGIC CORRELATION OF THE IDIOPATHIC HYPEREOSINOPHILIC SYNDROME. I. HEMATOLOGIC MANIFESTATIONS.

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Blood; 58(5):1012-1020 1981

A retrospective blind study of 32 patients with the hypereosinophilic syndrome was undertaken utilizing a hematologic scoring system that was based on peripheral blood and bone marrow findings, cytogenetics, B12 levels, and WBC alkaline phosphatase determinations. In addition to the grading system, which allowed formulation of a hematologic score, the data could also be normalized for indivi duals who did not have all tests performed by use of the hematologic quotient. This study clearly defined two groups of patients within the idiopathic hypereosinophilic syndrome. One group were those individuals with low hematologic scores and quotients who did not require therapy or who responded to prednisone therapy, while the second group of patients required cytotoxic therapy. These patients had significantly higher hematologic scores and quotients and a significant number of abnormalities similar to those seen in myeloproliferative syndromes, such as myelofibrosis and cytogenetic abnormalities. This types of hematologic scoring seems useful in predicting therapy and/or evaluating individuals or groups of patients with the hypereosinophilic syndrome. (Author abstract) (36 Refs)

10. CLINICAL-HEMATOLOGICAL AND CYTOGENETIC PARALLELS IN CHRONIC MYELOID LEUKEMIA.

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Clinical-Diagnostic Lab., All-Union Cancer Res. Center, Moscow, USSR
Ter Arkh; 53(9):20-25 1981

Results of comparative evaluation of morphological and cytochemical characteristics of blast cells are reported in a study of patients who had chronic myeloid leukemia (CML). Of 72 such patients studied, 20 had poorly differentiated blast cells, 26 showed myeloid differentiation of blast cells, 5 had promyelocytic variant of the blast crisis, 3 had monoblastic variant of the blast crisis, 2 had erythromegakaryocytic variant of the blast crisis, and 16 showed lymphoid differentiation of the blast cells. Karyotyping of blast cells was carried out in 40 of the patients. Additional aberration, involving chromosome 17, was detected in 2/11 patients with poorly differentiated variant, 12/16 with myeloblastic variant, and 1/2 with monoblastic variant. The most pronounced inhibition of hematopoiesis was observed in the patients with promyelocytic variant of CML. Of 20 patients with poorly differentiated CML, only 4 survived for greater than 5 yr, compared with 9/26 for those with myeloblastic CML, 2/5 for those with promyelocytic CML, 0/3 for those with monoblastic CML, 1/2 for those with erythromegakaryocytic CML, and 7/16 for those with lymphoblastic CML. (29 Refs) (In RUS)

11. TRANSLOCATION (5P;17Q) IN BLAST CRISIS OF CHRONIC MYELOID LEUKEMIA.

Hagemeijer A, Sizoo W, Smit EM, Abels J
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Cytogenet Cell Genet; 30(4):205-210 1981

A new abnormality of chromosome 17, distinct from i(17q), was observed in bone marrow cells of two patients with CML during a blast crisis. The marker was identified as a translocation of the short arm of chromosome 5 onto the long arm of chromosome 17, ie, t(5p;17q). In one case, the marker was clearly dicentric. The clinical history of these two patients showed some similarities. A slightly different marker has previously been observed in a cell line derived from a solid tumor. (Author abstract) (10 Refs)

12. PH1 CHROMOSOME IN CHRONIC MYELOID LEUKEMIA. DIAGNOSTIC AND PROGNOSTIC VALUE.

Labal de Vinuesa M, Brieux de Salum S
Instituto de Investigaciones Hematologicas, Academia Nacional de Medicina, Pacheco de Melo 3081, 1425 Buenos Aires, Argentina
Medicina (B Aires); 41(3):293-296 1981

The 48 myeloproliferative patients were examined for presence of Ph1 chromosome and/or other chromosomal anomalies: aneuploidy, translocation or deletion. Bone marrow samples were used to analyze 11-20 metaphases/patient. Of 48 patients, 11 who were later diagnosed as myelosclerosis, had no Ph1 chromosome, but various non specific aneuploidies. Ph1 chromosome was found only in chronic myeloid leukemia (CML) patients in agreement with Sandberg. Of 37 CML patients, 31 were Ph1+ with translocation t (9; 22) and 6 Ph1-. Survival time as well as peripheral blood leukocytes and platelets were increased in Ph1 + patients. Change in karyotype of one Ph1- patient with uncommon t (12; 13) preceded by 2 mo clinical signs of blast crisis. The importance of cytogenetic study in CML diagnosis and prognosis was stressed. (14 Refs) (In SPA)

13. ERYTHROBLASTIC TRANSFORMATION OF CHRONIC MYELOID LEUKEMIA: HYPERDIPLOID PH1-POSITIVE KARYOTYPES IN PRIMITIVE PAS-POSITIVE ERYTHROBLASTS.

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Blut; 42(6):345-354 1981

A case report of erythroblastic transformation of chronic myeloid leukemia (CML) is reported. Sternal bone marrow smears were analyzed morphologically, cytochemically, and cytogenetically, and clinical signs were evaluated at three times during the erythroblastic phase of Ph1-positive (Ph1+) disease. At diagnosis early erythroblasts (E1 + E2) accounted for 48% of nucleated marrow cells. This decreased to 5% during partial remission and increased to 7% during relapse. At diagnosis 85% of E1 + E2 cells were PAS-positive (PAS+). This decreased to 60% during remission, but increased to earlier levels during relapse. At diagnosis 14/50 metaphase cells were Ph1+ hyperdiploid (HD), including 11 with 50 chromosomes, 2 with 48, and 1 with 47. During remission no HD Ph1+ metaphases were found; 2/29 metaphases were pseudodiploid. During relapse 2/59 Ph1+ metaphases were HD, both with 47 chromosomes; one pseudodiploid was found. HD karyotypes varied in phase with the frequency of erythroblast mitosis and inversely with granulopoietic mitosis. The frequency of Ph1+ E1 + E2 corresponded to the frequency of Ph1+ HD metaphases. (22 Refs)

14. CYTOGENETIC CONVERSION FOLLOWING ALLOGENEIC BONE MARROW TRANSPLANTATION FOR ADVA NCED CHRONIC MYELOGENOUS LEUKEMIA.

McGlave PB, Miller WJ, Hurd DD, Arthur DC, Kim T
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Blood; 58(5):1050-1052 1981

We performed a pilot study to test the effectiveness of allogeneic bone marrow transplantation in the treatment of chronic myelogenous leukemia. Five patients in the advanced stages of chronic myelogenous leukemia (4 in blast crisis, 1 in accelerated phase) with abnormal chromosomes underwent matched-sibling allogeneic bone marrow transplantation after preparation with busulfan, vincristine, cyclophosphamide, and fractionated total body irradiation. Engraftment and conversion to normal chromosome patterns after transplantation occurred in all five patients. None of the patients reverted to an abnormal chromosome pattern or demonstrated clinical or hematologic evidence of recurrent disease during the course of this study; however, longest survival from transplant was 248 days. Allogeneic bone marrow transplantation can eradicate the abnormal clone even in far advanced chronic myelogenous leukemia and can provide normal hematopoiesis. We suggest that clinical complications of chemotherapeutic toxicity and infection were responsible for the short survival in this group of patients, and that these complications could be decreased by performing transplantation in the chronic phase or early accelerated phase of the disease. (Author abstract) (11 Refs)

15. ON THE 5Q- DELETION: CLINICAL AND CYTOGENETIC OBSERVATIONS IN TEN PATIENTS AND REVIEW OF THE LITERATURE.

Swolin B, Weinfeld A, Ridell B, Waldenstrom J, Westin J
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Blood; 58(5):986-993 1981

Clinical and cytogenetic findings in 10 patients with deletions of the long arm of chromosome 5 (5q-) are reported. Five cases had refractory anemia, the preleukemic syndrome, or refractory anemia with an excess of blasts; in all but one, the 5q- was the single initial abnormality. Three patients had overt leukemia; in all, the 5q- was accompanied by additional anomalies. Two patients had a myeloproliferative disorder. In one of these, a case of polycythemia vera, the 5q- appeared secondarily to other karyotypic abnormalities and concomitantly with transformation into a 'spent phase'. The deletions were interstitial in most cases, and even if the size of the deletion varied, the region q15-q31 was lost in all cases except two. Bone marrow from all cases except one showed a marked increase in the number of megakaryocytes. A survey of the literature yielded a total of 69 evaluable patients with 5q- deletions, including the present series. The 5q- has now been observed in a wide spectrum of hematologic disorders. However, most cases had either preleukemia (39%) or leukemia (46%). When detected during preleukemia, the 5q- usually appeared alone (74%), while during overt leukemia it regularly was accompanied by other abnormalities (88%). (Author abstract) (51 Refs)

DNA CONTENT AND PLOIDY CHANGES ASSOCIATED WITH CANCER

16. CYTOPHOTOMETRIC ANALYSIS OF HUMAN COLON, STOMACH, AND LIVER CANCER LINES TRANSPLANTED INTO ATHYMIC MICE. COMMUNICATION I.

Revazova ES, Petrova AS, Zubrikhina GN, Iudicheva TV
All-Union Cancer Res. Center, Moscow, USSR
Lab Delo; (9):550-552 1981

The results of cytophotometric analysis of DNA content in cells of human colon, stomach, and liver cancer lines transplanted into athymic BALB/c mice are reported. Majority of cells of xenografted colon carcinoma were characterized by diploid DNA content. Stomach cancer xenograft contained both the diploid (25.6%) and triploid (34.7%) cells. The greatest heterogeneity of DNA content was recorded in liver cancer xenografts. (8 Refs) (In RUS)

17. FLOW CYTOFLUOROMETRIC DNA ANALYSES ON METASTASES OF HUMAN MALIGNANT MELANOMA (MEETING ABSTRACT).

Hansson J, Tribukait B, Lewensohn R, Ringborg U
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Third European Workshop on Melanin Pigmentation, September 28-October 1, 1981, Prague, Czechoslovakia. Czechoslovak Medical Society 128 pp., 1981.

Flow cytofluorometric analyses of DNA content was performed on cells from 38 sc and lymph node metastases from 32 patients with malignant melanoma. Thirty tumors yielded only one cell population, while 8 tumors contained two or more cell populations. Cells from 8 tumors had DNA patterns corresponding to diploid DNA values and the remaining 30 had aneuploid cell populations, mostly in the diploid to tetraploid region. No significant correlation between cellular DNA content and patient survival was observed. The proportion of S-phase cells was calculated from DNA histograms of cells obtained from 25 metastases in 21 patients. The number of S-phase cells varied from 3-34%. The number of S-phase cells was significantly higher in aneuploid as compared to diploid cell populations. Patients with a proportion of S-phase cells greater than or equal to 10% had a significantly shorter survival time as compared to patients with S-phase cells less than 10% (p less than 0.025). (no Refs)

18. FLOW CYTOMETRIC DNA ANALYSIS OF ANAL CANAL EPITHELIUM AND ANO-RECTAL TUMORS.

Fenger C, Bichel P
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Acta Pathol Microbiol Scand [A]; 89(5):351-355 1981

Flow cytometric DNA analysis was performed on mucosal biopsies from the various epithelial types normally present in the anal canal, ie, colo-rectal epithelium, ATZ-epithelium and squamous epithelium as well as from rectal and anal adenocarcinomas and squamous carcinomas of the anal canal. Normal colo-rectal mucosa show homogenous cell populations with diploid DNA values, while adenocarcinomas contain diploid as well as aneuploid cell populations, regardless of location in the rectum or in the anal canal. The ATZ-epithelium shows a dominating normoploid population with a small 'hyperdiploid' peak. Polyploid nuclei were not found. The findings indicate that the ATZ-epithelium is related to metaplastic epithelium rather than to urothelium. The variants of squamos carcinoma in this study were rather poorly differentiated, but the FCM analysis showed a near diploid population with a high proliferative activity. The number of cases, however, is too small to be conclusive. (Author abstract) (24 Refs)

19. DISTRIBUTION OF NUCLEAR SIZE AND DNA CONTENT IN SERIAL LIVER BIOPSIES OF RATS TREATED WITH N-NITROSOMORPHOLINE, PHENOBARBITAL AND BUTYLATED HYDROXYTOLUENE.

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Exp Cell Biol; 49(6):294-305 1981

Nuclear size distribution and DNA content distribution were determined in liver biopsies of rats using an electronic particle counter and an impulse cytophotometer, respectively. Nuclear size distribution and DNA content distribution were found to be highly correlated regardless whether peak areas or peak heights of the histograms were compared. Treatment with the hepatocarcinogen N-Nitrosomorpholine (NNM) caused a dose-dependent increase in octoploid nuclei and a shift of the 2 n:4 n ratio in favor of the diploid nuclei. Treatment with Pb and BHT had minor effects on nuclear size and DNA content distribution. The paper demonstrates the usefulness of fine-needle aspiration biopsy procedure for the evaluation of liver changes induced by chemical substances. (Author abstract) (13 Refs)

20. DEFINITION OF PRECURSORS.

Fu YS, Reagan JW, Richart RM

Inst. Pathology, Case Western Reserve Univ., Cleveland, OH, 44106

Gynecol Oncol; 12(2,part2):S220-S231 1981

In this retrospective study of 100 cases of cervical intraepithelial abnormalities, the nuclear DNA content was correlated with the histologic findings and follow-up data. All cases had initial biopsies and were followed for more than a year with cytologic and/or histologic examinations. Of the 34 cases having a subsequent normal follow-up, 29 (85%) had a euploid or polyploid pattern and 5 (15%) had an aneuploid distribution. Of the 58 cases persisting as cervical intraepithelial neoplasia (CIN), 3 (5%) had a polyploid pattern and 55 (95%) had an aneuploid distribution. Of the eight cases which progressed to invasive carcinomas, all had an aneuploid pattern. These findings suggest that euploid or polyploid lesions are more likely to have normal follow-up studies (91%) and rarely persist (9%). Of the an euploid lesions, 81% persisted as CIN, 12% progressed to invasive carcinoma, and 7% had a normal follow-up. The presence of abnormal mitoses was the most reliable histologic criterion for aneuploidy. By using nuclear DNA analysis and histologic features, as defined in this study, it is possible to distinguish aneuploid precursors from less significant euploid or polyploid lesions. (Author abstract) (21 Refs)

CHROMOSOMAL FRAGILITY AND GENETIC FACTORS PREDISPOSING TO HUMAN CANCER

21. IMMUNOPATHOLOGY OF THE X-LINKED LYMPHOPROLIFERATIVE SYNDROME.

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Haematol Blood Transfus; 26:207-214 1981

Immunopathologic studies of affected individuals and carrier females from 25 kindreds exhibiting the X-linked lymphoproliferative syndrome (XLP) were carried out. XLP is a combined, variable immune deficiency with four phenotypes, all apparently triggered by Epstein-Barr virus (EBV) infection: (1) fatal infectious mononucleosis (IM), (2) chronic IM progressive to malignant lymphoma, (3) acute IM progressive to acquired agammaglobulinemia, and (4) malignant lymphoma. The clinical and pathological manifestations of XLP mimic the graft-versus-host reaction. Cytogenetic studies have revealed a spectrum from no appreciable defects to extensive aneuploidy in both peripheral lymphocytes and early passage lymphocytic lymphosarcoma cells; both affected and carrier individuals show a propensity to chromosome damage. Only weakly reactive anti-EBV antibodies are found, and anti-EBV nuclear antigen is lacking in affected individuals. Specific histopathology of the four phenotypes is discussed. These findings support the hypothesis that in XLP an immune deficiency toward EBV permits chronic and fatal lymphoproliferative responses to EBV infection. If this hypothesis is accurate, genetic counseling, providing of high titer gamma globulin, and antiviral therapy may be of prophylactic use. (58 Refs)

22. HUMAN TRIPLOIDY: ASSOCIATION WITH PARTIAL HYDATIDIFORM MOLES AND NONMOLAR CONCEPTUSES.

Szulman AE, Philippe E, Boue JG, Boue A
Dept. Pathology, Magee-Womens Hosp., Univ. Pittsburgh, Forbes Ave. and Halket St., Pittsburgh, PA, 15213

Hum Pathol; 12(11):1016-1021 1981

A retrospective pathologic review of nearly 100 spontaneous abortions of cytogenetically verified triploid constitution revealed a majority (86%) falling within the category of partial hydatidiform mole, the chief criteria being focal syncytiotrophoblastic hyperplasia, focal villous edema leading to cistern formation, scalloped outline of villi, and frequent 'trophoblastic inclusion' formation. The minority (14%) of the conceptuses were nonmolar with a normal or hypoplastic trophoblast. The triploid fetuses in both groups tended to die at about 8 wk menstrual age. Intrauterine retention was generally prolonged in the partial moles, whereas nonmolar conceptuses tended to abort within the first trimester, often with live or recently dead fetuses. The problem of two distinct morphologic entities within triploidy remains to be further investigated, especially with respect to the etiologic factors responsible for the division. (Author abstract) (30 Refs)

23. PRIMARY MYELOFIBROSIS WITH MYELOID METAPLASIA AND CYTOGENETICALLY ABNORMAL CLONES IN 2 CHILDREN WITH DOWN'S SYNDROME.

Ueda K, Kawaguchi Y, Kodama M, Tanaka Y, Usui T, Kamada N
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Scand J Haematol; 27(3):152-158 1981

Two children with Down's syndrome showed severe anemia, leukocytosis with blastic cells, thrombocytopenia and hepatosplenomegaly. Bone marrow aspirations were near-dry tap and marrow biopsy revealed primary myelofibrosis with myeloid metaplasia (MMM). Their course was short with a blood picture similar to that of leukemia. They expired 2 mo and 2 1/2 mo after diagnosis, respectively. The cases were thought to represent an acute childhood variant of MMM. Cytogenetic study of circulating white cells by 24 hr culture without phytohemagglutinin stimulation revealed aneuploidy in both cases, the first case showing marked aneuploidy with a predominant karyotype of 50,XX,+8,+19,+19,+21 and the second case a mosaic of 47,XX,+G/48,XX,+G,+G. The karyotype of phytohemagglutinin stimulated lymphocytes was 47,XX,+G in both cases. These findings suggest that the abnormal karyotypes are those of circulating blastic cells which are abnormal clones of hematopoietic cells responsible for MMM. In Down's syndrome, MMM might not be so rare as reported. (Author abstract) (20 Refs)

24. DOWN SYNDROME AND ACUTE LEUKAEMIA: INCREASED RISK MAY BE DUE TO TRISOMY 21.

Rowley JD
Section Hematology/Oncology, Dept. Medicine, Univ. Chicago, Chicago, IL, 60637

Lancet; 2(8254):1020-1022 1981

Individuals with Down syndrome (DS), especially children, have an increased incidence of acute leukemia. It is suggested that this increased risk is specifically associated with the presence of an extra chromosome 21 (+21) as a constitutional abnormality. Data available from surveys of non-DS patients with acute lymphocytic leukemia (ALL) and acute non-lymphocytic leukemia (ANLL) indicate that a +21 is the most common change in leukemic cells in ALL, especially in children, and that it is one of the more common changes in ANLL. In neonatal patients with mosaicism for normal cells and +21 cells who have a transient leukemoid reaction, the blast cells involve the +21 clone; spontaneous disappearance of the leukemoid reaction parallels a decrease in +21 cells in the bone marrow. Thus, the increased risk of acute leukemia in patients with DS who have a +21 is directly related to the presence, in all cells of these individuals, of the same chromosome change that is commonly seen in the leukemic cells of children with ALL, the type of leukemia most commonly seen in DS children. This observation is analogous to that for two other constitutional chromosome abnormalities that are associated with an increased risk of a malignant tumor. A deletion of chromosome 13, including band 13q14 is associated with retinoblastoma, and a deletion of chromosome 11, including band 11p13 is associated with aniridia/Wilms tumor syndrome. The nature of the genes affected by these various chromosome aberrations is unknown. (Author abstract) (20 Refs)

25. ACUTE LEUKAEMIA AND THE SAME CHROMOSOME ABNORMALITY IN MONOZYGOTIC TWINS.

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Hum Genet; 58(4):408-410 1981

Two monozygous twins with a 47,XX,+19 karyotype were diagnosed as having acute lymphoblastic leukemia at the age of 17 mo and 36 mo, respectively. Both patients presented with a history of pallor and bruising. Aggressive chemotherapy failed to produce remission in twin I and was abandoned and exchanged for supportive prednisolone treatment in twin II. Twin II also possessed a few cells with 46,XX,-11,-Abn karyotype. These cases provide evidence for in utero transformation. (15 Refs)

26. ABNORMALITIES OF HUMAN CHROMOSOME 13 AND IN VITRO RADIOSENSITIVITY. A STUDY OF 19 FIBROBLAST STRAINS.

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Mutat Res; 84(1):157-167 1981

In vitro radiosensitivity was studied in 19 strains of fibroblasts derived from patients with abnormalities of chromosome 13, including 7 with interstitial deletions, 2 with terminal deletions, 4 with complete trisomies, 3 with partial trisomies, 2 with inversions, and 1 with a translocation. Cultures were exposed to at least four doses/culture. Doses ranged from 50 to 900 rads. An unusually wide range of sensitivities (D0: 70-220 rads) was exhibited by the strains. Sensitivities of 132-152 rads had been reported for strains with abnormalities of other autosomes. One strain with complete trisomy of chromosome 13 had the greatest radioresistance reported. Sensitivities of strains bearing deletions distal to locus 13q14 were similar to sensitivities of normal cells. Chromosome 13 apparently is involved in cytotoxicity of x-irradiation. The specific location of this involvement appears to be at 13q14. (27 Refs)

27. FAMILIAL LEUKEMIA: PH1 POSITIVE ACUTE LYMPHOID LEUKEMIA OF A MOTHER AND HER INFANT.

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Blut; 43(4):265-272 1981

Acute lymphoid leukemia (ALL) was diagnosed in a mother and her 9-mo-old infant. The mother's symptoms (paleness, weakness, anemia) began during the second half of pregnancy. The mother achieved a short remission but died 15 mo after diagnosis. The infant remained in remission 23 mo after diagnosis. Both leukemia process were of 'O' cell character (mother: RBC-rosette forming cells:37%, cells with surface immunoglobulins: 2%, and non-T non-B-cells: 61%; infant: 18%, 10%, and 72%). The infant was human leukocyte antigen-identical with one of her healthy brothers, and haplo-identical with the other. Both ALL were Philadelphia chromosome (Ph1)-positive. During remission, Ph1 disappeared temporarily. In mo 17 of disease, the infant's bone marrow showed a normal karyotype. (35 Refs)

28. CLINICAL AND ENDOCRINE SPECTRUM IN PATIENTS WITH THE 45,X/46,XY KARYOTYPE.

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Hum Genet; 58(4):373-376 1981

The correlation between gonadal morphology, endocrine dynamics, phenotypic expression, and cytogenetics was studied in five unrelated patients (3 male, 2 female, 6-20 yr old) with 45,X/46,XY karyotypes. The external phenotypic characteristics of the patients are described. Three of the patients developed gonadoblastomas, one in the ectopic testis (Patient C), one from a streak gonad (Patient A), and one from ovarian stroma (Patient B). The X-chromatin was negative in all patients. Karyotypic results are presented. Two patients (Patients C and D) showed abnormal non-fluorescent Y chromosomes. Persistently elevated serum gonadotropins were found in Patients A and B. Administration of luteinizing hormone (LH)-releasing hormone (LH-RH)induced induced significant increase in both LH and follicle stimulating hormone (FSH) in both patients. Serum testosterone (T) levels were extremely low and did not respond to human chorionic gonadotropin (HCG) stimulation. In Patient A, serum androstenedione was 0.45 nanog/ml and showed significant increase following HCG stimulation. Elevated LH and FSH levels with normal LH-RH response were found in Patient C. Circulating T levels were within normal lower values. HCG administration induced subnormal although significant increase in serum T. Low LH and FSH levels with normal pituitary LH-RH responsiveness were found in Patient D. Serum T levels were detectable but below normal. HCG stimulation produced a small but significant increase in serum T. Patient E had normal LH and FSH serum levels. LH-RH stimulation significantly increase LH levels. Serum T levels were extremely low with a diminished but significant response to HCG. The results show the clinical variability of patients with 45,X/46,XY karyotype. (13 Refs)

29. FAMILIAL MYELOPROLIFERATIVE DISEASE. HEMATOLOGICAL AND CYTOGENETIC STUDIES.

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Acta Med Scand; 210(4):321-327 1981

A family is described in which a form of myeloproliferative disease involving the megakaryocytic cell line occurs in three generations, resulting in thrombocytosis in several members. An autosomal dominant transmission with variable penetrance is proposed, based on the distribution of involved members in the pedigree. Two family members appeared to have an abnormal chromosome 7, which is frequently observed in patients with hematological disorders. It is our opinion that the chromosomal aberration is primarily related to the mutagenicity of the cytostatic treatment, although a primary defect cannot be fully excluded. (Author abstract) (24 Refs)

30. SCE ANALYSIS IN PATIENTS WITH 'FAMILIAL' MALIGNANT MELANOMA (MEETING ABSTRACT).

Illeni MT, Ghidoni A, Privitera E, Rovini D, Vaglini M, Cascinelli N
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Third European Workshop on Melanin Pigmentation, September 28-October 1, 1981, Prague, Czechoslovakia. Czechoslovak Medical Society 128 pp., 1981.

The sister chromatid exchange (SCE) analysis is not commonly employed to detect malignant tumors and precancerous lesions or to identify cancer prone subjects; the only exception is represented by the Bloom syndrome. However, some papers have recently appeared in which higher SCE/cell values are evidenced in patients with different neoplastic conditions (Ph, positive leukemia, malignant lymphoma, retinoblastoma and multiple nevoid basal cell carcinoma) or in subjects who, for other familial neoplastic diseases can be considered as particularly prone to cancer. The present work was intended to study the SCE frequency in patients with 'familial' malignant melanoma. Brother and sister with melanoma were studied, two healthy brothers being the controls. In the same way another familial group, father and two sons, was analyzed, and compared to healthy collateral. The results indicate, for each family a significantly higher frequency of SCE/cell in melanoma patients vs/their collateral. The two familial groups greatly differ with regard to the overall SCE/cell. This result suggests that different etiological factors may be involved in these familial conditions. (no Refs)

31. ANIRIDIA AND WILMS' TUMOR (MILLER'S SYNDROME).

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Klin Paediatr; 193(3):238 1981

Aniridia is frequently associated with Wilms' tumor, indicating that the two disorders are part of a syndrome (Miller's syndrome). The syndrome also involves facultative genital malformation, mental retardation, and microcephaly. Chromosome analysis indicates an interstitial deletion in the short arm of chromosome 11. Oncological observation of patients with aniridia is urged. (4 Refs) (In GER)

32. SCLERODERMA AND ESOPHAGEAL CARCINOMA: CHROMOSOMAL ABNORMALITIES IN A PATIENT.

Nissenblatt MJ, Ludwig S, Feinsmith N, Sciorra L
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NY State J Med; 81(12):1748-1750 1981

A link between progressive systemic sclerosis (PSS) and neoplasia is suspected. Scleroderma is a chromosomal breakage syndrome. A case history is presented of a patient with esophageal carcinoma diagnosed 14 mo after clinical onset of PSS. Chromosome aberrations (CA) were demonstrated in somatic cells. A causal relationship between CA and neoplasia is suggested. (20 Refs)

33. A HIGH INCIDENCE OF MITOTIC CHIASMATA IN ENDOREDUPLICATED BLOOM'S SYNDROME CELLS.

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Hum Genet; 58(4):417-421 1981

Chiasma frequency in Bloom's syndrome (BS) diplochromosomes was compared with that in diplochromosomes of Fanconi's anemia (FA) and normal cells. Fibroblast cultures were initiated from a skin biopsy of a male BS patient (3 yr old). Lymphocytes were cultured from a male FA patient (9 yr old). Mitotic chiasma were identified by the clear change from pairing of sister chromatids to pairing of chromatids attached to different centromeres and by the clear continuity of both chromatids at the point of crossing. Among non-endoreduplicated BS cells, only approx 0.5% of diploid cells contained chiasma compared to 16% of the near-tetraploid cells. Among endoreduplicated cells with a near-diploid number of diplochromosomes, approx 2.5 chiasmata/cell were found. Of 37 endoreduplication cells with a near-diploid number of diplochromosomes found in BS fibroblasts, 21 were suitable for mitotic chiasmata analysis. Of 19 diploid endoreduplicated cells found in FA lymphocytes, 13 were analyzable for chiasmata. Approx 3.4-5.4x as many chiasmata per diplochromosome were found in BS cells as in FA cells. By all three methods of analysis (total number of chiasmata, number of chiasmata and probable chiasmata, and av number of chiasmata per diplochromosome), BS diplochromosomes contained significantly more chiasmata than FA diplochromosomes. Homologous, isolocal, asymmetrical quadriradicals were examined in BS and FA cells. Only two chiasmata were found in diploid BS fibroblasts, one in an F chromosome and one in a C. The distribution of chiasmata among chromosomes in the endoreduplicated cells, in which chiasma frequency was proportional to chromosome length, differed significantly from the non-random distribution of chiasmata in chromosomes of diploid BS lymphocytes. BS chromsomes apparently have a greater tendency to undergo mitotic exchange than normal or FA cells. (19 Refs)

34. MUTAGEN-INDUCED SISTER CHROMATID EXCHANGE RATE IN BLOOM SYNDROME REMAINS UNALTERED IN THE PRESENCE OF BLOOM CORRECTIVE FACTOR.

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Hum Genet; 58(4):432-433 1981

The ability of the soluble corrective factor (CF), produced by normal cultured fibroblasts, to reduce mutagen-induced sister chromatid exchange (SCE) was studied in lymphocytes from Bloom syndrome (BS) patients after ethylmethanesulfonate, mitomycin C, or 4-nitroquinoline-1-oxide exposure. CF reduced the spontaneously increased SCE in BS cells by approx 20 SCE/metaphase but failed to reduce the additional mutagen-induced SCE increase. (6 Refs)

35. THE ATAXIA TELANGIECTASIA CLASTOGENIC FACTOR IS A LOW MOLECULAR WEIGHT PEPTIDE.

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Dept. Human Genetics, Hadassah-Hebrew Univ. Medical Center, Jerusalem, Israel
Hum Genet; 58(4):422-424 1981

The ataxia telangiectasia (AT) clastogenic factor in plasma and in conditioned medium from cultured AT skin fibroblasts was found to be a peptide of mol wt in the range 500-1,000 dalton. The factor was present in plasma and in conditioned medium from AT fibroblasts but could not be detected in homogenates of AT fibroblasts. Different factors capable of causing chromosome breakage in normal peripheral lymphocytes may be produced in patients with spontaneous chromosome breakage. (11 Refs)

36. ABNORMAL REGULATION OF DNA REPLICATION AND INCREASED LETHALITY IN ATAXIA TELANGIECTASIA CELLS EXPOSED TO CARCINOGENIC AGENTS.

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Cancer Res; 42(1):335-341 1982

The effect of different carcinogenic agents on the rate of semiconservative DNA replication in normal human and ataxia telangiectasia (AT) cells was investigated. The rate of DNA synthesis in all AT cell strains tested was depressed to a significantly lesser extent than in normal cells after exposure to x-rays under oxia or hypoxia or to bleomycin, agents to which AT cells are hypersensitive. In contrast, inhibition of DNA replication in normal human and AT cells was similar after treatment with some DNA-methylating agents or mitomycin C. Colony-forming ability of AT cells treated with these agents was not different from normal cells. Treatment with 4-nitroquinoline 1-oxide elicited a variable response in both AT and normal cell strains. In some strains, including those shown to be hypersensitive to the drug by other workers, the inhibition of DNA synthesis was more pronounced than in other cell strains, but no significant difference between AT and normal cells could be detected. The rejoining of DNA strand breaks induced by x-rays, measured by DNA elution techniques, occurred within 2 hr after treatment and could not be correlated with the difference in DNA synthesis inhibition in AT and normal cells. After low doses of x-rays, AT cells rejoined single-strand breaks slightly more slowly than did normal cells. The rate of DNA replication in x-irradiated AT and normal cells was not affected by nicotinamide, an inhibitor of poly(adenosine diphosphate ribose) synthesis. These data indicate that the diminished inhibition of DNA replication in carcinogen-treated AT cells (a) is a general characteristic of all AT cell strains, (b) correlates with AT cellular hypersensitivity, (c) is not directly caused by the bulk of the DNA strand breaks produced by carcinogenic agents, and (d) is not based on differences in the induction of poly(adenosine diphosphate ribose) synthesis between x-irradiated AT and normal cells. (Author abstract) (47 Refs)

37. RADIORESISTANT DNA SYNTHESIS: AN INTRINSIC FEATURE OF ATAXIA TELANGIECTASIA.

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Mutat Res; 84(1):183-190 1981

Radioresistance of DNA synthesis (DNAS) was compared in normal human diploid cells of cell line HS27 and six strains derived from patients with ataxia telangiectasia (AT). Three of the AT cell lines had previously been classified as proficient in repair replication after gamma-irradiation. Inhibition of DNAS was measured by incorporation of 14C-thymidine. Cells of normal and AT lines were exposed to 0-5,000 rads of x-rays. To determine the rate of DNAS at various times after irradiation, cultures were pulse-labeled at various times after irradiation. DNAS was strongly inhibited by up to 1,000 rads in HS27, but not in AT cells. DNAS was inhibited to a lesser extent between 1,000 and 5,000 rads in both HS27 and AT cells. In HS27 cells DNAS was reduced to approx 35% of control values for 1 hr, increasing to 60% from 2 to 4 hr after irradiation. In AT cells DNAS was reduced to 75-80% of control values 90 min after irradiation and remained at that level after 4 hr. Inhibition of replicon initiation was the primary factor in radioresistance of AT cells. Chain elongation was also more radioresistant in AT cells than in HS27 cells. Up to 2,000 rads inhibition of DNAS in AT cells was due almost entirely to inhibition of replicon initiation and not of chain elongation. (17 Refs)

CHROMOSOMES OF HUMAN CELL LINES AND TUMORS IN VITRO

38. PH(1)-NEGATIVE T LYMPHOCYTIC COLONIES IN AGAR CULTURES OF PERIPHERAL BLOOD IN CHRONIC MYELOID LEUKEMIA.

Bagnara GP, Biagini G, Marani M, Bonsi L, Severi B, Valvassori L, Comis M, Nobile F, Iacopino P, Ronco F, Neri A
Instituti di Isotologia ed Embriologia Generale e, Universita di Bologna, Italia
Acta Haematol (Basel); 66(3):174-180 1981

T lymphocytic colony formation by peripheral lymphocytes separated by discontinuous albumin gradient centrifugation was evaluated in eight patients with Philadelphia (Ph(1))-positive chronic myeloid leukemia (CML). Colonies were obtained using a liquid-on-agar culture system recently introduced (PHA overlayer-WBC feeder layer assay) which has been shown to be simple and reliable. The pattern of colony growth in CML and in normal controls was similar, the peak ranging from the 4th to the 6th day. Also the morphological aspects of colonies did not differ in the two groups. Cells recovered from CML lymphocytic colonies were shown to belong to T cell lineage, as they are able to form spontaneous E-rosettes and to respond to mitogenic stimulation in vitro. In contrast, cells recovered from all other cultured fractions failed to display these properties. Cytogenetic analysis showed that T colony cells were Ph(1)-negative whereas the chromosome anomaly was found in nonlymphoid colonies of the same patients, thus suggesting a nonclonal origin of T lymphocytes in CML. (Author abstract) (25 Refs)

39. CYTOGENETEIC ANALYSIS OF HUMAN MALIGNANT MELANOMA CELL LINES. RELATION TO TUMORIGENICITY IN NUDE MICE (MEETING ABSTRACT).

Bertrand S, Jacubovich R, Cabrillat H, Leftheriotis E, Dore JF
INSERM U218, Lyon, France
Third European Workshop on Melanin Pigmentation, September 28-October 1, 1981, Prague, Czechoslovakia. Czechoslovak Medical Society 128 pp., 1981.

On 36 cell lines, derived from human melanomas and obtained from 31 patients, karyotype analyses, utilizing banding techniques were carried out. Gross aneuploidy was seen in all mitoses. Majority of cell lines had modal distribution near triploidy. All cell lines derived from different individuals were identifiable by their marker chromosomes. When multiple cell lines were derived from a single biopsy specimen or from two different lesions of the same patient, common marker chromosomes were always observed. Markers, common to all of the mitoses of a given cell line, were identifiable over several mo or yr in culture, thus denoting stability of these markers. Interesting features appeared when the cytogenetic studies of 10 melanoma lines were compared to their ability to grow in athymic nude mice. We determined the number of copies of normal chromosomes and their involvement in the constitution of markers. Highly tumorigenic cell lines had majority of their mitoses characterized by either numerous copies or (and) involvement of chromosomes 3, 7, 16, 22 in the constitution of markers and relatively few copies of chromosome 9. On the contrary poorly tumorigenic cell lines had majority of their mitosis characterized by either few copies or relatively infrequent involvement of chromosomes 3, 7, 16, 22 in the constitution of markers, but a relatively high number of chromosome 9. Cell lines with intermediate tumorigenicity were shown to contain several subpopulations characterized by mitoses containing either numerous or few copies of chromosomes 3, 7, 16, 22 and 9. (no Refs)

40. HETEROTRANSPLANTATION OF HUMAN MALIGNANT MELANOMA CELL LINES IN NUDE MICE (MEETING ABSTRACT).

Dore JF, Jacubovich R, Cabrillat H, Bertrand S
INSERM U 218, Centre Leon Berard, Lyon, France
Third European Workshop on Melanin Pigmentation, September 28-October 1, 1981, Prague, Czechoslovakia. Czechoslovak Medical Society 128 pp., 1981.

Human malignant melanoma cell lines have been shown to be heterogenous and may contain cell populations differing in their growth potential and/or susceptibility to host reaction. To further investigate this heterogeneity, 10 melanoma cell lines were transplanted into 6-8 wk old outbred nude mice. Seven of these lines gave 50-100% tumor takes within 2 mo, but for the 3 other lines the tumor take never exceeded 25%. However these latter lines can grow within one wk in nude mice previously irradiated or ip injected with silica particles. The admixture of BCG to cells from highly tumorigenic lines reduces the tumor take down to 10-20%; this effect being proportional to the amount of BCG (100 to 500 ug) and inversely proportional to the number of grafted cells. The pretreatment of nude mice by irradiation does not modify the effect of BCG on the graft of highly tumorigenic cell lines and enables to observe this effect on the graft of cells from a poorly tumorigenic cell line. On the other hand, pretreatment of nude mice with silica reduces the effect of BCG on the graft of an highly tumorigenic line, but does not modify this effect when a poorly tumorigenic line is grafted. Cytogenetic studies were performed on cells recultured from tumors obtained after heterotransplantation in untreated nude mice: when a highly tumorigenic line of male origin in which 52% of metaphases contained one Y chromosome was transplanted, only 8.3% of the mitoses of the recultured cells had kept the Y chromosome; when a poorly tumorigenic line was transplanted, the cytogenetic analysis of recultured cells showed that only cells containing numerous copies of chromosomes 3, 7, 16 and 22 and lacking chromosome 9 had successfully grown. (no Refs)

CHROMOSOMES OF ANIMAL CELL LINES AND TUMORS

41. THE ROLE OF CHROMOSOME 15 IN MURINE LEUKEMOGENESIS. I. CONTRASTING BEHAVIOR OF THE TUMOR VS. NORMAL PARENT-DERIVED CHROMOSOMES NO. 15 IN SOMATIC HYBRIDS OF VARYING TUMORIGENICITY.

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Dept. Tumor Biology, Karolinska Inst., S-104 01 Stockholm, Sweden
Int J Cancer; 28(6):785-798 1981

G-banding analysis was carried out on a series of hybrids derived from the fusion of a chromosome 15-trisomic murine T-cell leukemia of AKR origin and normal diploid fibroblasts or lymphocytes of the CBT6T6 strain. Due to the 14;15 translocation involved in the generation of the T6 marker, the chromosomes No 15 and 14 derived from the normal and the tumor parent can be distinguished cytogenetically. Highly tumorigenic, in vitro maintained hybrids, and high-tumorigenic segregants of originally low-tumorigenic in vitro hybrids, selected by in vivo passage, showed a similar cytogenetic pattern. It was characterized by the amplification of the tumor-derived chromosome No 15 from the expected 3 to 5.5 +-0.2 copies and a concomitant decrease of the normal derived T(14;15)6 from two copies to 0.9 +-0.2. All other autosomes except No 14 showed only minor random variations, around the expected number of four copies. The tumor-derived chromosome 14 was amplified from the expected two to three copies. The low-tumorigenic hybrids showed the opposite pattern with a decrease in the number of the tumor-derived 15 chromosome from 3 to 2.6 +-0.1 and the maintenance of the two normal parent derived T(14;15)6 chromosomes. These findings suggest the existence of a qualitative difference between the 15 chromosomes derived from the tumor vs the normal parent, due to mutation or proviral DNA insertion in the tumor-derived homologue. Amplification of the changed locus and a decrease in the dosage of its normal counterpart appear to favor tumorigenicity. (Author abstract) (20 Refs)

42 THE ROLE OF GENE DOSAGE AND GENETIC TRANSPOSITIONS IN CARCINOGENESIS.

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Nature; 293(5839):313-318 1981

Analysis of chromosome translocations associated with B-cell derived tumors and studies of chromosome-15 trisomy in murine leukemia support the theory, emerging from recent work on tumor viruses, that cancer can be associated with DNA rearrangements which result in the increased expression of normal cellular genes. (Author abstract) (87 Refs)

43. CYTOGENETIC ANALYSIS OF THE L5178Y/TK+/- [LEADS TO]TK-/- MOUSE LYMPHOMA MUTAGENESIS ASSAY SYSTEM.

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Mutat Res; 84(1):169-181 1981

The L5178Y/TK+/- mouse lymphoma cell line and its TK-/- mutants, which are used in the L5178Y/TK+/-[leads to]TK-/- mutagen assay (TKMA), are characterized. Mutagenesis in this system produces two cell types lacking thymidine kinase (TK) activity (TK-/-) types: large-colony (lambda) and small-colony (sigma) forms. The parental TK+/- heterozygote cells have a stable karyotype, characterized by the presence of normal mouse chromosomes and recognizable rearrangements. Lambda cells have essentially the same karyotype as the heterozygote cells. Sigma clones show considerable chromosome rearrangement, particularly involving one chromosome 11. Analysis of chromosome rearrangements suggests that lambda cells have lost TK activity as the result o a point mutation, while sigma cells have lost it due to chromosomal events. The TKMA evidently can detect both point mutations and chromosomal rearrangements involving the TK locus. (18 Refs)

44. CORRELATION OF CHROMOSOMAL ABERRATION IN A MYELOMA CELL LINE WITH TUMORIGENICITY IN NUDE MICE.

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Blut; 43(2):93-97 1981

The relationship between chromosomal aberrations in the monoclonal myeloma cell line L 363 and tumorigenicity in nude mice was examined. The karyotype of the L363 cell line was 49,X, +7,-5,-8,-22, +t(1q;8q), +t(1q;8q), +t(8; 5q), +t(8; 5q), mar VIII, + mar IX, 6q-, Xq-, 14q+. Only when this clone (A) was transplanted with a feeder cell population, was tumors induced in the nude mouse brain. The recultivated intracranial tumor cell population shared identical chromosomal pattern with the original in vitro cell line. A new subclone (B) of the L363 cell line was demonstrated in 3% of metaphases, which showed the loss of one translocation chromosome 1. At that time intracranial nude mouse transplantation together with feeder cells induced tumors consisting of 73% clone A and 27% subclone B cells. The increase of subclone B by nude mouse passage demonstrated the growth advantage of this clone. A new intracranial transplantation of the mixed in vitro population (A and B) without feeder population resulted in growth of only subclone B cells. The myeloma cells gained tumorigenicity in the nude mouse brain by loss of one translocation chromosome (-t). The karyotype of the in vitro recultivated monoclonal cell line from the tumor (subclone B) remained constant. During 10 mo, subclone B increased from 3% to 80% in the permanent culture. Another transplantation of Clones A (90%) and B (10%) resulted in a new chromosomal marker (1q-, breakpoint in 1q31) characterizing clones C and D. Thus, specific chromosomal changes inducing tumorigenicity of the myeloma cell line in nude mice were demonstrated. (11 Refs)

GENE MAPPING STUDIES

45. THE SITE OF INTEGRATION OF THE HERPES SIMPLEX VIRUS TYPE 1 THYMIDINE KINASE GENE IN HUMAN CELLS TRANSFORMED BY AN HSV-1 DNA FRAGMENT.

Kit S, Hazen M, Otsuka H, Qavi H, Trkula D, Dubbs DR
Div. Biochemical Virology, Baylor Coll. Medicine, Houston, TX, 77030
Int J Cancer; 28(6):767-776 1981

To analyze the site of integration of the herpes simplex virus Type I (HSV-I) thymidine kinase (TK) gene in biochemically transformed human cells, TK- HeLa(BU25) cells were transformed to the TK+ phenotype by a cloned, 2 kbp PvuII fragment of HSV-1 DNA. The transformed cells [HeLa(BU25)/TF pAGO PP3] were fused with mouse LM(TK-) cells, and human-mouse somatic cell hybrid clones (LH PP3 clones 1, 2, 3, 5 and 6) were isolated in HATG-ouabain selective medium. The HeLa(BU25)/TF pAGO PP3 cells and the LH PP3 hybrid clones expressed HSV-1-specific TK activity and a herpesvirus-associated nuclear antigen, and contained herpesvirus nucleotide sequences. Molecular hybridization experiments were carried out to map the HSV-I and flanking cellular nucleotide sequences in the biochemically transformed cells. TK- revertant subclones isolated by growing the LH PP3 clone 5 cells in BrdUrd (and diphtheria toxin) failed to form colonies in HATG medium, but retained HSV-I nucleotide sequences. Isozyme analyses on 21 gene-enzyme systems representing 21 human chromosomes revealed that all of the LH PP3 clonal lines expressed human hexosaminidase B, which has been assigned to chromosome 5, and all were sensitive to diphtheria toxin, which is also a marker for chromosome 5. Chromosome analyses showed that chromosome 5 was the only human chromosome present in mitoses of LH PP3 clone 5 cells and that human chromosome 5 was present in most of the mitoses of LH PP3 clone 1, 2, 3, and 6 cells. The latter clones also contained 1 or 2 additional human chromosomes in some of the cells. As expected from the molecular hybridization analyses, TK- revertants of LH PP3 clone 5 cells retained portions of chromosome 5 and expressed human hexosaminidase B. The results indicate that HSV-I nucleotide sequences were stably integrated in the biochemically transformed cells, most likely in human chromosome 5. (50 Refs)

46. IMMUNOGLOBULIN HEAVY CHAIN GENES IN HUMANS ARE LOCATED IN CHROMOSOME 14.

Hobart MJ, Rabbitts TH, Goodfellow PN, Solomon E, Chambers S, Spurr N, Povey S

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Ann Hum Genet; 45(4):331-335 1981

Human chromosomes were segregated by developing mouse-human somatic cell hybrids. DNA from these hybrids was cleaved by restriction endonucleases and assessed for presence of human immunoglobulin heavy chain constant and variable region genes. The heavy chain gene complex was located on chromosome 14. (20 Refs)

47. ASSIGNMENT OF THE GENES FOR HUMAN LAMBDA IMMUNOGLOBULIN CHAINS TO CHROMOSOME 22.

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Nature; 293(5837):173-175 1981

Somatic cell hybrids between mouse myeloma cells and either human peripheral lymphocytes or different human lambda chain-secreting lymphoblastoid cell lines were studied. Mouse x human hybridomas were pre-selected for the expression of human lambda chains; it was determined that only human chromosomes 14 and 22 were likely to carry the human lambda heavy-chain genes. To exclude the possibility that the human lambda-chain genes were located on chromosome 14 and confirm their assignment to chromosome 22, five independent lambda chain-secreting clones were subcloned and studied for expression of human lambda chains and isozyme markers assigned to each of the different human chromosomes. Chromosome 14 was excluded from consideration: two subclones lost chromosome 14 yet retained the ability to produce lambda chains. Results confirmed that the genes for lambda chains were on chromosome 22; the chromosome was the only human chromosome consistently present in all subclones secreting human lambda chains. Loss of human chromosome 22 resulted in loss of the ability to produce human lambda chains. (18 Refs)

48. MAPPING OF IMMUNOGLOBULIN VARIABLE REGION GENES: RELATIONSHIP TO THE 'DELETION' MODEL OF IMMUNOGLOBULIN GENE REARRANGEMENT.

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Nucleic Acids Res; 9(21):5725-5735 1981

Five families of variable region genes of mouse kappa chains were analyzed by Southern blot hybridization to determine their relative chromosomal map positions. Map positions were deduced by Vkappa gene deletion from antibody-producing cells expressing upstream Vkappa genes and retention in cells expressing downstream genes. The Vkappa regions expressed in the myelomas MOPC167, MPC11, MOPC21 and ABPC20 are members of Vkappa families exhibiting one, three, six and six major germline hybridization bands respectively. The gene order of the five families in germline DNA was found to be VM167-VM11-(VM21, VA20) - VABE8-Jkappa - Ckappa. As expected in a deletion model of Ig gene rearrangement, a sequence located just 5' of J1 in germline DNA was found to be absent from some antibody producing cells which had not retained any germline Ckappa genes. However, other cell lines contained this sequence in rearranged contexts, suggesting that any deletion model of Ig V-J joining, as well as V gene mapping, must take into account the possibilities of stepwise rearrangements and reintegration of 'deleted' DNA. (Author abstract) (17 Refs)

49. A NEW MOUSE CELL-SURFACE ANTIGEN (LY-M20) CONTROLLED BY A GENE LINKED TO MLS LOCUS AND DEFINED BY MONOCLONAL ANTIBODIES.

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Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Immunogenetics; 14(1/2):3-14 1981

Five monoclonal antibodies were established by the fusion of mouse myeloma cells (NS.1) with spleen cells from A and (A x C3H/An)F1 mice hyperimmunized with 70Z/3 tumor cells. These antibodies recognized a new antigenic specificity provisionally called Ly-m20.2. In direct cytotoxicity assays, 60% of cells in spleen, 40% in lymph node, 50% in bone marrow and less than 5% in thymus were found to react with three of the five antibodies, whereas the two others yielded somewhat lower cytotoxicity indices. The Ly-m20.2 antigen was also expressed on cells derived from liver and kidney but not on cells derived from brain. As judged from cytotoxicity assays with separated T and B cells, Ly-m20.2 antigen is carried preferentially on B lymphocytes. Direct plaque-forming cells were completely eliminated by Ly-m20.2-specific antibody and complement. Linkage tests by analysis in 20 (CBA/J x C3H/An) x C3H/An backcross mice and by segregation analysis of BXH and SWXL recombinant inbred strains indicate close association of the loci controlling ly-m20.2 and Mls antigens on chromosome 1. (Author abstract) (30 Refs)

50. GENETIC CONTROL OF CROSS-REACTIVE CYTOTOXIC T-LYMPHOCYTE RESPONSES TO A BALB/C TUMOR.

Russell JH, Dobos CB, Graff RJ, Taylor BA
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Immunogenetics; 14(3/4):263-272 1981

Using a segregation analysis we have determined that the cross-reactive response to the DBA/2 tumor P815 by CTL from BALB/c mice immunized with a BALB/c plasmacytoma (MOPC-167) is controlled by a single gene. The gene responsible is closely linked to the dilute coat color locus on chromosome 9. In contrast, the cross-reactive response to the DBA/2 tumor L5178Y by DBA/2 anti-MOPC-167 CTL appears to be controlled by two or more genes. (Author abstract) (24 Refs)

MOLECULAR CYTOGENETICS

51. UNSTABLE AMPLIFICATION OF AN ALTERED DIHYDROFOLATE REDUCTASE GENE ASSOCIATED WITH DOUBLE-MINUTE CHROMOSOMES.

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Dept. Biological Sciences, Stanford Univ., Stanford, CA, 94305
Cell; 26(3,part1):355-362 1981

We have studied a line of 3T6 mouse fibroblasts grown in progressively increasing concentrations of methotrexate. Initially, drug resistance results from amplification of the gene encoding the normal dihydrofolate reductase. Growth of these methotrexate-resistant populations at higher methotrexate concentrations results in the emergence of cells expressing high levels of dihydrofolate reductase with a reduced methotrexate affinity. Using the fluorescence-activated cell sorter, we demonstrate that the variant gene is not present in the population of cells resistant to lower levels of methotrexate, and hence we postulate that the mutational event occurred in cells already containing multiple normal dihydrofolate reductase genes. Growth of the variant cells in the absence of selection is associated with the permanent loss of the altered genes and the disappearance of double-minute chromosomes, on which these genes reside. The pattern of accumulation and loss of double-minute chromosomes is reproduced following transformation of methotrexate-sensitive cells with the altered genes. Our results are consistent with autonomous replication of double-minute chromosomes and a selective advantage of cells with the smallest number of extrachromosomal elements necessary for survival at a given methotrexate concentration. (Author abstract) (26 Refs)

52. COMPARISON BETWEEN THE VIRAL TRANSFORMING GENE (SRC) OF RECOVERED AVIAN SARCOMA VIRUS AND ITS CELLULAR HOMOLOG.

Takeya T, Hanafusa H, Junghans RP, Ju G, Skalka AM
Rockefeller Univ., New York, NY, 10021
Mol Cell Biol; 1(11):1024-1037 1981

To gain information on the relationship between the src region of Rous sarcoma virus (RSV) (v-RSV) and cellular src (c-src), and clues to the origins of recovered avian sarcoma viruses (rASV), molecular clones were isolated containing src related sequences from the parental RSV, from rASV, and from c-src, the presumed progenitor of rASV. Molecular clones of viral DNA from rASV and its transformation-competent progenitor, the Schmidt-Ruppin A strain of RSV were constructed and analyzed. A 2.0-megadalton EcoRI fragment, containing the entire src gene from each of the clones was subcloned and characterized. The fragments were also used as probes to isolate recombinant phage clones containing the cellular counterpart of the viral src gene (c-src), from a lambda library of chicken DNA. Restriction endonuclease mapping of c-src revealed extensive similarity between the src region of RSV and rAVS, but striking differences between viral src's and c-src. Electron microscopic analysis of heteroduplexes between recovered virus src and c-src revealed a 1.8-kilobase homologous region. In the cellular gene, the homologous region was interrupted by seven nonhomologous region which is interpreted to be intervening sequences. Minimum length of c-src is estimated at 7.2 kilobases. The findings have implications concerning the mechanism of formation of recovered virus src and possibly other cell-derived retrovirus transforming genes. (58 Refs)

53. REPLICATION OF VIRAL DNA SEQUENCES INTEGRATED WITHIN THE CHROMATIN OF SV40-TRANSFORMED CHINESE HAMSTER LUNG CELLS.

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Div. Biology, Kansas State Univ., Manhattan, KS, 66506
Cell; 26(2,part2):245-258 1981

To determine when during S phase integrated viral DNA sequences in several tsA SV40-transformed Chinese hamster cell clones replicate, we pulse-labeled cultures with BrdUrd and subsequently collected mitotic cells during sequential time intervals. Restriction endonuclease mapping indicated that each of the three SV40-transformed Chinese hamster lung cell clones contained a single viral DNA sequence at a different, but in each case unique, chromosomal site. DNA was extracted from each population of mitotic cells and then was resolved into dense, BrdUrd-containing and light, unsubstituted DNA fractions by cesium chloride gradient centrifugation. In each pair of samples obtained, we measured viral DNA sequences by soln hybridization using single-stranded SV40 32P-labeled DNA probes. Our results support the conclusions that specific genes within a mammalian DNA are programmed to replicate at particular times during S phase, and that the SV40 A gene product, large T antigen, programs integrated viral DNA sequences to replicate very early in S phase. The fractions of viral DNA replicated early in S phase appeared to correlate with each clone's content of functional large T antigen at permissive and nonpermissive culture temperatures. (Author abstract) (96 Refs)

54. RESTRICTION OF REPLICATION OF ROUS SARCOMA VIRUS MEDIATED BY THE SRC REGION OF THE GENOME: ANALYSIS OF THE FORMATION AND INTEGRATION OF VIRAL DNA AND THE EFFECTS OF CONDITIONAL AND NONCONDITIONAL MUTATIONS IN SRC.

Neiman PE, Stone J, Gilbert L, Fincham VJ, McMillin-Helsel C, Wyke JA
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Virology; 114(2):516-525 1981

The growth of most Rous sarcoma viruses (RSV) is severely restricted on MSB-1 cells (a line of chicken T lymphoblasts) in comparison to growth on chicken embryo fibroblasts (CEF). Nonconditional transformation defective mutants of RSV from which the complete src region has been deleted (td RSV) are not subject to growth restriction. We examined the formation and integration of RSV and td RSV in MSB-1 cells following high multiplicity infection. Nearly equivalent quantities of the linear form of unintegrated RSV and td RSV DNA were formed in these cells during the first 10 hr after infection. Linear RSV DNA from MSB-1 cells could not be distinguished from linear RSV from CEF by restriction endonuclease analysis and by previously described transfection assays. Beyond 10 hr after infection, and with progressive cell growth in the MSB-1 cultures, the level of RSV linear DNA rapidly decreased. Presumptive circular RSV DNA was detected only transiently, and at very low levels, about 15 hr after infection. Association of RSV DNA with high-mol wt chromosomal DNA, ie, integration, was not detected in this study. In contrast, nearly constant levels of td RSV unintegrated linear DNA and, after 20 hr, circular DNA persisted in MSB-1 cells for at least 7 days after infection. Integration of td RSV proviral DNA was inefficient, occurring in only about 5% of MSB-1 cells (even at very high multiplicities of infection) in the first round of infection, and in 25-40% of cells by 3 days after infection. Almost all MSB-1 cells contained td RSV DNA produced virus. Analysis of eight nonconditional transformation defective mutants of RSV which retain the src region to different extents showed that all of these mutants replicated to the same normal titer on MSB-1 cells as on CEF without further deletion of the src region. Two temperature sensitive src mutants of RSV showed similar growth restriction on MSB-1 cells at both 35 C and 41 C, indicating that thermal inactivation of the src gene product could not abrogate the replication block. These studies clearly demonstrate that the presence of the src region in RSV impedes the formation and/or integration of provirus in some types of host cells. (Author abstract) (24 Refs)

55. DISTRIBUTION OF DNA-BOUND CARCINOGEN 4-NITROQUINOLINE 1-OXIDE AND OF REPAIR-SYNTHESIZED DNA IN CHROMATIN OF WI-38 CELLS.

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Cancer Lett; 14(2):205-215 1981

Distribution within chromatin of the binding sites of 4-nitroquinoline-1-oxide (NQ) was investigated. Binding of NQ to nucleic acids of cells treated in vitro (WI-38 human diploid fibroblasts) reached a plateau by 90 min at a concentration of 1 x 10(-5) M. The specific activity of (3H)NQ bound to DNA did not change significantly during digestion with DNAase I, whereas it decreased with increasing degradation of DNA by micrococcal nuclease. These results suggest that NQ preferentially binds to nucleosomal linker DNA; no correlation is apparent between transcriptional activity of chromatin and binding of NQ to DNA. When the distribution of repair-synthesized DNA in chromatin damaged by NQ was studied, (3H)thymidine incorporated into repaired DNA was found to be more sensitive to nucleases but distributed approx equally among chromatin subfractions of differing transcriptional activity. (35 Refs)

56. LOCALIZATION OF DNA METHYLTRANSFERASE IN THE CHROMATIN OF FRIEND ERYTHROLEUKEMIA CELLS.

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Nucleic Acids Res; 9(20):5359-5381 1981

Chromatin fragments released from intact Friend erythroleukemia cell nuclei during limited incubation with micrococcal nuclease, DNase II or DNase I were analyzed to determine the distribution of DNA methyltransferase in chromatin. The enzyme was released in a free form when internucleosomal DNA was digested with micrococcal nuclease but was found associated with Mg++-precipitable polynucleosomes after DNase II digestion. Less than 25% of the enzyme was released from nuclei incubated with DNase I under conditions where transcriptionally active chromatin should have been completely digested. These results indicated that the bulk of DNA methyltransferase was bound to 'linker' DNA in condensed regions of chromatin. Preferential rebinding of free enzyme to linker DNA was also demonstrated in vitro. The possibility that chromatin proteins play a role in regulating access of DNA methyltransferase to specific sites in DNA is discussed in light of these findings. (Author abstract) (38 Refs)

57. KINETICS OF O6-METHYLGUANINE REPAIR IN HUMAN NORMAL AND ATAXIA TELANGIECTASIA CELL LINES AND CORRELATION OF REPAIR CAPACITY WITH CELLULAR SENSITIVITY TO METHYLATING AGENTS.

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Cancer Res; 41(12):5114-5120 1981

Human lymphoblastoid cell lines from normal individuals and from patients with ataxia telangiectasia were either proficient or deficient in their ability to repair the mutagenic DNA adduct O6-methylguanine that is induced by methylating carcinogens. There was no relationship between the capacity to repair O6-methylguanine and the ataxia telangiectasia phenotype. Time-course studies done following a short pulse (2 min) of alkylation with 0.5 mg of N-[3H]methyl-N'-nitro-N-nitrosoguanidine per ml revealed that the repair of O6-methylguanine in human lymphoblastoid lines proficient in this ability is a rapid process, which proceeds with a half-life of 10 to 15 min. Lymphoblastoid lines with deficient capacity to repair this DNA adduct were hypersensitive to the cytotoxic effect of the methylating carcinogens N-methyl-N'-nitro-N-nitrosoguanidine, N-methyl-N-nitrosourea, and methyl methanesulfonate, and this hypersensitivity was correlated with the relative amount of O6-methylguanine induced by each of the three chemicals. This was taken as an indication of the lethality of unrepaired O6-methylguanine. The extent of DNA repair synthesis induced by the three carcinogens was the same in cell lines proficient and deficient in O6-methylguanine repair, indicating no major deficiency in an excision repair pathway in the hypersensitive cell lines. (Author abstract) (44 Refs)

58. DNA FORK DISPLACEMENT RATES IN HUMAN CELLS.

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Biochim Biophys Acta; 656(1):36-39 1981

DNA fork displacement rates were measured in 20 human cell lines by a bromodeoxyuridine-313 nm photolysis technique. Cell lines included representatives of normal diploid, Fanconi's anemia, ataxia telangiectasia, xeroderma pigmentosum, trisomy-21 and several transformed lines. The av value for all the cell lines was 0.53 +-0.08 um/min. The av value for individual cell lines, however, displayed a 30% variation. Less than 10% of variation in the fork displacement rate appears to be due to the experimental technique; the remainder is probably due to true variation among the cell types and to culture conditions. (Author abstract) (14 Refs)

59. REPAIR OF PSORALEN-TREATED DNA BY GENETIC RECOMBINATION IN HUMAN CELLS INFECTED WITH HERPES SIMPLEX VIRUS.

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Cancer Res; 41(12):5033-5038 1981

Herpes simplex virus type 1 was treated with 4,5',8-trimethylpsoralen (psoralen) plus near-UV light in order to produce lesions (monoadducts and DNA cross-links) in the viral DNA. Human fibroblasts were infected by damaged virus under conditions in which either a single virus particle or several particles entered a given cell, and the fraction of virus-producing cells was determined. This fraction was significantly greater for multiply infected cells than for singly infected cells, indicating that the psoralen lesions are repaired more efficiently in the presence of homologous, damaged DNA (multiplicity reactivation). Evidence is presented that herpes simplex virus may code for functions which participate in its own repair, both during multiplicity reactivation and during repair which occurs in singly infected cells: (a) host cells deficient in repair of lesions induced by psoralen (xeroderma pigmentosum) or the DNA cross-linking agent mitomycin C (Fanconi's anemia) exhibited normal levels of multiplicity reactivation of psoralen-treated herpes virus; (b) while xeroderma pigmentosum cells have been previously shown to be deficient in repair of psoralen-treated adenovirus under conditions of single infection, herpes virus is repaired at near normal levels in these same cells. Recombination levels between genetically marked pairs of herpes viruses were found to increase after treatment of the parental viruses with psoralen, suggesting that psoralen damage stimulates genetic recombination. This stimulation provides convincing evidence for a repair pathway in which genetic recombination between damaged viral genomes can lead to the production of viable virus. (Author abstract) (28 Refs)

60. EXCISION REPAIR OF AFLATOXIN B1-DNA ADDUCTS IN HUMAN FIBROBLASTS.

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Cancer Res; 41(12):5125-5129 1981

The processing of covalent aflatoxin B1 (AFB1)-DNA adducts was investigated in confluent normal fibroblasts (NF) and xeroderma pigmentosum skin fibroblasts of Complementation Group A (XPA) following treatment with rat liver microsome-activated A1 for 30 min. Following rapid DNA isolation at slightly acidic pH by a new filter technique, more than 90% of the adducts corresponded to 2,3-dihydro-2-(N7-guanyl)-3-hydroxy-AFB1 (AFB1-N7-Gua) according to the analysis of acid hydrolysates by high-pressure liquid chromatography. The changes in adduct concentration and composition were compared between DNA isolated immediately following AFB1 treatment and incubated at neutrality in vitro and DNA in situ in the cell isolated after different lengths of incubation. The following conclusions were reached from the observed differences in the kinetics of adduct removal from free DNA and DNA in situ in NF and XPA: (a) AFB1-N7-Gua is removed spontaneously and enzymatically in NF but probably only spontaneously in XPA. This result suggests that these lesions are removed via nucleotide excision repair in NF; (b) the putative 2,3-dihydro-2-(N5-formyl-2',5',6'-triamino-4'-oxo-N5 pyrimidyl)-3-hydroxyaflatoxin B1 from AFB1-N7-Gua in vitro and in situ in the cell. It accumulates more rapidly and to a greater extent in XPA than in NF and persists in both cell types over prolonged periods. The reaction of A1-N2-Gua to 2,3-dihydro-2-(N5-formyl-2',5',6'-triamino-4'-oxo-N5 pyrimidyl)-3-hydroxyaflatoxin B1 represents the transformation of a repairable lesion to a non-repairable, persistent lesion. (Author abstract) (25 Refs)

61. EFFECT OF ACTIVATORS OF CAMP ACCUMULATION ON DIFFERENT STAGES OF GENOME EXPRESSION DURING ACUTE RADIATION INJURY. COMMUNICATION 2. EFFECT OF SEROTONIN AND PAPAVERINE ON TEMPLATE ACTIVITY OF NUCLEAR CHROMATIN FROM LIVERS AND SPLEENS OF RATS SUBJECTED TO WHOLE-BODY X-IRRADIATION.

Tsudzevich BA, Galkina LA, Kucherenko NE
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Radiobiologiia; 21(5):654-659 1981

Administration of serotonin (ST) and papaverine (PV) to rats prior to whole-body x-irradiation prevented the inhibition of template activity of spleen chromatin and stimulated the template activity of liver chromatin. It was suggested that the radioprotective effect of activators of cyclic AMP is associated with increased radioresistance of early stages of genome expression. (11 Refs) (In RUS)

62. DETECTION OF DNA SINGLE-STRAND BREAKS PRODUCED DURING THE REPAIR OF DAMAGE BY DNA-PROTEIN CROSS-LINKING AGENTS.

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Cancer Res; 42(1):145-149 1982

In this investigation, the combination of 1-beta-D-arabinofuranosylcytosine and hydroxyurea was used to inhibit the polymerase step of DNA excision repair. The DNA single-strand breaks (SSB), which accumulated in the presence of these agents, were measured by alkaline elution. With this approach, DNA SSB were detected in normal human fibroblasts after exposure to trans-platinum(II)diamminedichloride, formaldehyde or potassium chromate. These agents all share the common feature in that they induce DNA-protein cross-links in mammalian cells. In the case of trans-platinum(II)diamminedichloride or formaldehyde, the frequency of these SSB was markedly less in excision-deficient xeroderma pigmentosum cells. With chromate, a high level of SSB was induced in both normal and xeroderma pigmentosum cells; these results indicate that chromate damage to DNA is repaired by a mechanism different than the classical excision pathway since xeroderma pigmentosum cells responded normally. Several other agents were investigated with this approach, and no SSB were detected with nickel sulfate, 12-O-tetradecanoylphorbol-13-acetate or asbestos fibers in the p resence or absence of the polymerase inhibitor. This approach was found to be a very sensitive method to detect DNA excision repair. (Author abstract) (21 Refs)

63. THE DISTRIBUTION OF BENZO(A)PYRENE DNA ADDUCTS IN MAMMALIAN CHROMATIN.

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Nucleic Acids Res; 9(21):5533-5552 1981

This paper describes the distribution of DNA-lesions generated by the potent carcinogen benzo(a)pyrene (BP) or its ultimate metabolic derivative 7alpha,8beta,di-hydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene (BPDE) within mammalian chromatin using the enzymic probe micrococcal nuclease. We have shown that the progress of the nuclease on naked DNA is unaffected by the presence of the hydrocarbon lesion at moderate extents of digestion. Digestion of nuclei isolated from murine erythroleukemic cells immediately following BPDE treatment, and analysis of micrococcal nuclease resistant DNA by TCA precipitation, hydroxyapatite chromatography and gel electrophoresis demonstrates a non-random distribution of lesions. Approx 3x more binding occurs on the linker DNA regions between nucleosome cores than on the nucleosome core DNA itself. A similar result was obtained with BPDE treated primary mouse embryo cells; however nuclei isolated from these cells after prolonged treatment with BP (to allow metabolic activation) showed no such preferential binding. Post-treatment incubation of PBDE-treated cells shows that this difference can be accounted for by the loss of preferential localization with time. (Author abstract) (33 Refs)

EFFECTS OF EXOGENOUS AGENTS ON CHROMOSOMES

64. INVESTIGATIONS ON RADIOSENSITIVE AND RADIORESISTANT POPULATIONS OF DROSOPHILA MELANOGASTER. XIII. EFFECTS OF RADIORESISTANT MUTANTS (RAR) ON CHEMICAL (EMS) MUTAGENESIS.

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Institut fur Genetik, Freie Universitat Berlin, Berlin-Dahlem, W. Germany
Mutat Res; 103(1):87-90 1982

After treatment with ethyl methanesulfonate (EMS), treated Drosophila melanogaster males were mass mated to Basc females and treated D melanogaster females to males carrying Ys In(1)EN car f In(1)dl49 v y-YL/0. Sex-linked recessive lethals were scored as percentage of X-chromosomes tested, after treatment of various germ-cell stages of +K (normals), ROI/0, rar-3, and ROI/40 with EMS in various forms of application (injection or fed). Mutation frequencies indicated normal efficiency of EMS injection. High mutational yields from mature oocytes indicated a reasonable uptake of EMS after feeding and confirmed the marked sensitivity of stage-14 oocytes compared with stage-7 and younger oocytes. The low sensitivity of immature oocytes to EMS makes comparison between genotypes somewhat difficult. The system of relative ra dioresistance, which has evolved under the irradiation conditions of the populations ROI and ROI/4, is not based on specific radiobiological processes but involves more general pathways of mutagenesis. (13 Refs)

65. THE FIRST TWO MITOTIC CYCLES IN HUMAN LYMPHOCYTES IRRADIATED AT DIFFERENT STAGES.

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Res. Inst. Medical Radiology, Obninsk, USSR
Radiobiologiia; 21(5):712-715 1981

The effect of irradiation at different stages of cell division on the kinetics of the mitotic cycle was studied in human peripheral blood lymphocytes. The lymphocytes were irradiated with gamma rays (200 rads) during the G0, late G1, S, and G2 phases; duration of the first mitosis after irradiation was assessed by sister chromatid differential staining technique. Irradiation at G0 did not affect the duration of the first mitosis, irradiation at G1 and S increased the duration 4 hr, and irradiation at G2 increased the duration by 8 hr. (9 Refs) (In RUS)

66. CYTOGENETIC ASPECTS OF APPLICATION OF NEUTRONS IN RADIOTHERAPY. COMMUNICATION 2. BIOLOGICAL EFFECT OF 6.0 MEV FAST NEUTRONS.

Letov VN, Seredenko EA, Ievlev SM, Stavshaia SV
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Radiobiologiia; 21(5):752-755 1981

The yield of chromosome aberrations induced by 6-million-electron-volt fast neutrons was studied in a culture of human peripheral blood lymphocytes. The biological effectiveness of fast neutrons was found to depend upon dose rate, stage of cell cycle, and conditions of irradiation. (11 Refs) (In RUS)

67. CELL-STAGE-SPECIFIC ENHANCEMENT BY CAFFEINE OF THE FREQUENCY OF CHROMATID ABERRATIONS INDUCED BY X-RAYS IN NEURAL GANGLIA OF DROSOPHILA MELANOGASTER.

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Mutat Res; 84(1):91-99 1981

The effect of caffeine on chromatid aberrations induced by x-rays in neural ganglia of Drosophila melanogaster was studied. Ganglia were removed from third-instar larvae and treated with colchicine (10(-3) M) to accumulate cells in mitosis. They were then exposed to caffeine (10(-2) M), x-rays (500 R), or both. Caffeine alone produced high rates of chromatid aberrations only when added to cells late in G2 phase or during mitotic prophase. Although caffeine alone did not induce aberrations during S-phase, middle G-phase, or C-mitosis, it did enhance the damage produced by x-rays. This enhancement was similar in all three phases. During S- and G2-phases damage consisted primarily of isochromatid deletions and chromatid exchanges. Treatment during C-mitosis produced all types of chromatid damage. Enhancement of X-ray-induced damage may be due to inhibition of DNA repair mechanisms by caffeine. (25 Refs)

68. TUMOUR PROMOTERS INDUCE MITOTIC ANEUPLOIDY IN YEAST.

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Nature; 294(5838):263-265 1981

A series of seven phorbol analogues and eight unrelated compounds were tested for induction of aneuploidy or crossing-over in assays using the D6 strain of Saccharomyces cerevisiae. A positive response was a three-fold or greater increase in frequency of aneuploid colonies in at least two separate experiments. All promoters tested were positive, while nonpromoters were negative. 12-O-Tetradecanoylphorbol-13-acetate (TPA) and phorbol-12-13-didecanoate (PDD) were positive while no significant increases in aneuploidly were observed with phorbol, phorbol monoesters, 4-O-methyl-TPA or 4alpha-PDD, which are also inactive as promoters on mouse skin. A dose-response curve for TPA showed dose-related increases in aneuploidy over the concentration range 0.02-5.0 ug/ml. Mezerein, a weak promoter but as potent as TPA in inducing many biochemical and morphological effects in cells, did not induce aneuploidy in the assay. The tumor promoters had no effect on the frequency of crossing-over. However, under identical conditions, the incomplete promoter mezerein induced mitotic cross-over at concentrations greater than 10 ug/ml whereas TPA was ineffective. Mezerein was the only compound which showed significant activity in increasing cross-over. The data presented do not indicate whether the assay of induced chromosome aneuploidly in yeast will be useful in detection of tumor promoting chemicals. (27 Refs)

69. MITOMYCIN C- AND STREPTOZOTOCIN-INDUCED MOTILITY AND NUMERICAL SPERM VARIANTS IN MICE.

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Mutat Res; 90(3):287-295 1981

Mitomycin C, a cross-linking mutagen and clastogen, and streptozotocin, a point mutagen, were observed to decrease sperm motility and sperm count in treated male HA (ICR) mice and in their F1 progeny. These effects may result from gene mutations and/or chromosomal aberrations. (15 Refs)

70. CHROMOSOMAL DAMAGE INDUCED BY FUROCOUMARINS AND UVA IN HAMSTER AND HUMAN CELLS INCLUDING CELLS FROM PATIENTS WITH ATAXIA TELANGIECTASIA AND XERODERMA PIGMENTOSUM.

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Mutat Res; 84(1):113-124 1981

The relative capacities of four furocoumarins to sensitize cells to near-UV (UVA) were studied in Chinese hamster ovary cells (CHO) and human cells from normal, ataxia telangiectasia (AT), and xeroderma pigmentosum (XP) individuals. Cells were exposed in vitro to psoralen (PS), 5-methoxypsoralen (5MOP), 8-methoxypsoralen (8MOP), or angelicin (AN) at concentrations of 40 ug/ml. Cultures were irradiate d with UVA (320-380 nanometers). In CHO cells the most active substance was PS, followed in order by 8MOP, 5MOP, and AN. The first three produced DNA monoadducts and cross-links, but AN produced only adducts. All four compounds produced higher rates of sister chromatid exchanges (SCE) in AT and XP cells than in normal human cells. AN required high UVA doses to produce damage compared with 8MOP and 5MOP. Normal human cells were approx 2.3 times as sensitive to SCE production than CHO cells. Damage was of the type produced by UV or alkylating agents. Results indicate that 5MOP produces the same effects in human cells as the known carcinogen 8MOP. The use of 5MOP in suntan preparations should therefore not be permitted. (22 Refs)

71. MUTAGENIC EFFECT OF TRICHLORFON AND DIMETHOATE ON MOUSE MYELOCYTES IN VIVO.

Nehez M, Selypes A, Scheufler H
Kozegeszsegtani es Jarvanytani Inezet, Szegedi Orvostudomanyi Egyetem, Szeged, Hungary
Egeszsegtudomany; 25(3):262-266 1981

The mutagenic effects of trichlorfon (TF; 1 x 405 mg/kg ip) and dimethoate (1 x 20 or 1 x 60 mg/kg ip) were studied in male CFLP mice after 24 and 48 hr. Significant differences were found in the number of aberrant cells 24 and 48 hr after treatment with TF, and 24 and 48 hr after treatment with 60 mg/kg dimethoate. The number of aberrant cells 48 hr after TF treatment was 22/200 vs 5/200 in the controls (p less than 0.01). Numerical aberration was found in 1/200 cases (0/200 in the controls), chromatid gap in 21/200 (4/200 in the controls), and break in 0.200 (1/200 in the controls). The number of aberrant cells 48 hr after treatment with 60 mg/kg dimethoate was 51/200 (vs 6/200 in the controls): numerical aberration was found in 7/200 cases (vs 0/200 in the controls), chromatid type aberration in 35 (4 in the controls), and chromosome type aberration (acentric fragment and deletion) in 9 (in the controls). The findings suggest the possibility of the mutagenic effect of both substances. (26 Refs) (In HUN)

72. A COMPARATIVE GENOTOXICITY STUDY OF CHLOROGENIC ACID (3-O-CAFFEOYLQUINIC ACID).

Stich HF, Rosin MP, Wu CH, Powrie WD
Environmental Carcinogenesis Unit, British Columbia Cancer Res. Centre, 601 West 10th Avenue, Vancouver, British Columbia V6T 1W5
Mutat Res; 90(3):201-212 1981

Genotoxicity of chlorogenic acid was evaluated in three different bioassays that depend on different tester cells and endpoints: reverse mutation in Salmonella typhimurium, gene conversion in Saccharomyces cerevisiae, and chromosome aberration in Chinese hamster ovary cells (CHO). No significant increase in mutagenesis in either Salmonella tester strain TA98 or TA100 was observed with or without addition of S9 mixture. A significant increase in his+ reversion frequency occurred when the strains were exposed to a mixture containing both Mn++ and chlorogenic acid. Addition of Cu++ was without effect. Neither transition metal induced his+ revertants alone. Caffeic acid produced a similar response pattern, but quinic acid was not mutagenic even in the presence of Mn++. Chlorogenic acid induced a greater than 2x increase in tryptophan (trp+) conversion frequency at non-toxic concentrations. Presence of S9 suppressed the response and transition metals enhanced it. Chlorogenic acid was also found to be a direct acting clastogen. In the presence of Mn++, chromatid breaks and exchanges were induced by chlorogenic acid at doses 10x lower than required by chlorogenic acid alone. (31 Refs)

73. ISSUES RELEVANT TO THE ASSESSMENT OF CHEMICALLY INDUCED CHROMOSOME DAMAGE IN VIVO AND THEIR RELATIONSHIP TO CHEMICAL MUTAGENESIS.

Anderson D, Richardson CR
British Industrial Biological Res. Assoc., Woodmansterne Road, Carshalton, Surrey SM5 4DS, England
Mutat Res; 90(3):261-272 1981

Male Wistar rats were killed 6 or 24 hr after single or multiple exposure to clastogens, and bone marrow samples were prepared. Benzene, mitomycin C (MitC), ethyl methane sulfonate (EMS), trimethyl phosphate (TMP), and vinyl chloride (VC) constituted the groups of clastogens analyzed. A statistically significant increase in percentage of abnormal cells above negative control values, as well as some increases in individual categories of chromosome damage were observed after treatment with each clastogen. Dose-response relationships were evident for benzene, EMS, and MitC. For TMP and VC only one dose level was tested. Gap incidence increased above that of other types of chromosome damage. Multiple exposure at the same sampling time and with the same route of administration produced similar or smaller total amounts of chromosome damage than single exposure. Higher yields of damage were obtained at 6 hr than at 24 hr after treatment with benzene. Benzene also produced a similar level of damage after ip injection or a single 2 hr exposure by inhalation. (13 Refs)

74. EVALUATION OF THE CLASTOGENIC ACTION OF BENZENE BY ORAL ADMINISTRATION WITH 2 CYTOGENETIC TECHNIQUES IN MOUSE AND CHINESE HAMSTER.

Siou G, Conan L, El Haitem M
Laboratoire d'Histopathologie, C.E.R.T.I., 59 avenue de Paris, 78000 Versailles, France
Mutat Res; 90(3):273-278 1981

Metaphase chromosome studies and micronucleus counts of bone-marrow cells from Swiss mice and Chinese hamsters exposed to between 2 x 10.2 and 2 x 2,500 ul benzene/kg body wt po were conducted. After po administration of benzene to mice, the mean numbers of polychromatic RBC with micronuclei increased with dose from 2 x 25.6 ul benzene/kg. Male mice showed a greater sensitivity than females to micronucleus induction. In the same animals, benzene also increased the frequency of chromosomal aberrations. The increase became significant at 2 x 64 ul benzene/kg and increased with dose; males were more sensitive than females. A significant increase in number of micronuclei occurred at a lower dose than did frequency of metaphase chromosomal aberrations. After po administration of benzene to Chinese hamsters, the mean numbers of polychromatic RBC with micronuclei did not increase progressively with dose as in mice. Results obtained from analysis of metaphase chromosomes led to a similar conclusion: benzene does not have a clastogenic effect in Chinese hamsters. (23 Refs)

75. CHROMOSOME STUDIES OF PATIENTS ON LONG-TERM LITHIUM THERAPY FOR PSYCHIATRIC DISORDERS.

Garson OM, Latimer NZ, Chiu E, Dixon K
Cytogenetics Unit, Dept. Medicine, Univ. Melbourne, St. Vincent's Hosp., Fitzroy, Vic. 3065, Australia
Med J Aust; 2(1):37-39 1981

Chromosome studies, including sister chromatid exchange techniques, were performed on blood samples from 23 patients receiving long-term, continuous lithium therapy for psychiatric disorders. Nineteen healthy, age-matched individuals were used as controls. No increase in chromosome damage was detected, when samples from the lithium group were compared with the control group samples. (Author abstract) (17 Refs)

76. CYTOGENETIC STUDY OF WORKERS EXPOSED TO METHYL-PARATHION.

de Cassia Stocco R, Becak W, Gaeta R, Rabello-Gay MN
Servico de Genetica, Instituto Butantan, Caixa Postal 65, Sao Paulo, Brazil
Mutat Res; 103(1):71-76 1982

Cell aberrations were studied in a group of 15 subjects exposed to methyl-parathion (O,O-dimethyl-o,p-nitrophenyl phosphorothioate); subject cholinesterase levels were 75% or less of normal. Period of exposure varied from 1 wk to 7 yr, with intermittent periods of non-exposure. Controls were 13 men with 100% cholinesterase level who had not been occupationally exposed to any chemical and were of comparable age and socioeconomic status. The workers exposed to methyl-parathion did not show an increased frequency of chromosome aberrations in lymphocyte cultures compared to the non-exposed controls.

Considering that methyl-parathion is often contaminated with DDT (dichloro-diphenyl trichloroethane), seven exposed and eight control subjects were randomly assayed for DDT and its principal metabolite DDE (1,1-dichloro-2,2-bis[p-chlorophenyl]ethylene). Levels of DDT in exposed individuals did not differ significantly from those of controls. While it is known that increased chromosome aberrations occur in cases of acute intoxication, chronic exposure to small doses of methyl-parathion in the work place do not seem to produce the same effect. (16 Refs)

77. EFFECT OF HUMAN LEUKOCYTE INTERFERON ON HUMAN LYMPHOCYTES IN VITRO: CYTOGENETIC STUDIES.

Sorensen PJ, Jensen MK, Jersild C
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Mutat Res; 90(2):143-147 1981

In vitro effects of interferon (IF) on chromosomal stability in mitogen-stimulated peripheral blood lymphocytes from normal individuals were investigated. Although no increase in structural chromosome aberrations was found, the response of lymphocytes to various mitogens was inhibited by IF. (21 Refs)

78. FAILURE OF CHLOROFORM TO INDUCE CHROMOSOME DAMAGE OR SISTER-CHROMATID EXCHANGES IN CULTURED HUMAN LYMPHOCYTES AND FAILURE TO INDUCE REVERSION IN ESCHERICHIA COLI.

Kirkland DJ, Smith KL, Van Abbe NJ
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Food Cosmet Toxicol [illegible](5):651-656 1981

Mutagenicity of chloroform in Escherichia coli strains WP2p and WP2uvrA-p was tested using both plate incorporation and liquid pre-incubation. In addition, ability of chloroform to induce sister-chromatid exchanges (SCE) in human lymphocytes in the presence of S-9 rat-liver microsomes was tested. Chloroform did not induce reversions in WP2p or WP2urvA-p in either of the assays used. In contrast, both positive control chemicals used (N-methyl-N'-nitro-N-nitrosoguanidine and 2-aminoanthracene) were mutagenic. Benzo-(a)pyrene at concentrations up to 10 ug/ml induced significant increases in SCE in human lymphocytes in the presence or the absence of S-9, whereas chloroform (25-400 ug/ml) plus S-9 induced a significant increase in SCE in cells from the same donor only at the 50-ug/ml dose. Whereas the positive control gave reasonable dose-response trends [correlation coefficient (r) 0.995 and 0.782 with and without S-9, respectively], this was not the case for chloroform (r = 0.206). Failure of chloroform to induce any type of mutagenic event in vitro raises questions in relation to prediction of cancer risk. (19 Refs)

79. THE RELATIONSHIP BETWEEN THE CARCINOGENICITY AND MUTAGENICITY OF NITROSAMINES IN A HEPATOCYTE-MEDIATED MUTAGENICITY ASSAY.

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Carcinogenesis; 2(10):1075-1077 1981

The hepatocyte-mediated mammalian cell mutagenesis assay was used to determine the mutagenic activity of 26 nitrosamines for which a carcinogenic potency could also be established. Mutagenesis was measured in Chinese hamster V79 cells cocultivated with primary rat hepatocytes, which are capable of activating nitrosamines. Resistance to ouabain and to 6-thioguanine served as genetic markers. Carcinogenicity data were obtained from experiments in which groups of male and female Fischer rats were treated with nitrosamines po for 50 wk. A linear relationship between carcinogenicity and mutagenicity was established (p = 0.000!). The correlation coefficients at the 6-thioguanine and the ouabain markers were 0.85 and 0.66, respectively. This study demonstrates that the use of intact hepatocytes to activate nitrosamines, coupled with appropriate mammalian target cells to indicate genetic damage, represents a useful system for both detecting and establishing the mutagenicity of a series of nitrosamines in a manner corresponding to the carcinogenic potency produced by the same chemicals in vivo. (24 Refs)

80. CORRELATIONS OF DNA DAMAGE AND REPAIR WITH NUCLEAR AND CHROMOSOMAL DAMAGE IN HELA CELLS CAUSED BY METHYLNITROSAMIDES.

Collins AR, Ord MJ, Johnson RT
Cancer Res. Campaign Mammalian Cell DNA Repair Group, Dept. Zoology, Univ. Cambridge, Downing St., Cambridge, CB2 3EJ, England
Cancer Res; 41(12):5176-5187 1981

N-Methyl-N-nitrosourethan induces breaks or alkali-labile sites in cellular DNA, many if not all of which are repaired rapidly. Other DNA lesions are repaired by an excision process. Hydroxyurea and 1-beta-d-arabinofuranosylcytosine cause an accumulation of DNA breaks after N-methyl-N-nitrosourethan treatment, probably by inhibiting the DNA-synthetic (but not the nucleolytic) stage of excision repair. Chromosome damage (fragmentation or attenuation of interphase chromosomes and decondensation and radial rearrangement of metaphase chromosomes) is present soon after treatment with N-methyl-N-nitrosourethan and is not reversed during further incubation. It is apparently associated with the longer-lived DNA lesions, probably those which are removed by excision, and is enhanced by incubation with hydroxyurea and 1-beta-d-arabinofuranosylcytosine. N-Methyl-N-nitrosourethan also inhibits cellular protein and DNA synthesis and causes the dispersion of polysomes and the loss of nucleolar structure. N-Methyl-N-nitrosourea is less potent than N-methyl-N-nitrosourethan in causing DNA or chromosome damage and is less cytotoxic. (Author abstract) (72 Refs)

81. DNA-DAMAGE IN HUMAN CELLS TREATED WITH THE CLOSELY RELATED ALKYLATING AGENTS PEPTICHEMIO, M-L-SARCOLYSIN AND MELPHALAN.

Ringborg U, Lambert B, Lewensohn R, Turesson I
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Eur J Cancer Clin Oncol; 17(9):991-996 1981

In vitro experiments were performed on human peripheral WBC to compare DNA repair synthesis induced by peptichemio (a multipeptide complex containing m-L-sarcolysin), m-L-sarcolysin and melphalan. The peptide bound m-L-sarcolysin gave rise to max DNA repair synthesis at a concentration interval between 1 x 10(-5) and 3 x 10(-5) M as opposed to a concentration interval of 3 x 10(-4) to 1 x 10(-3) M for melphalan. The peptide bound m-L-sarcolysin induced DNA repair synthesis at similar molar concentrations to m-L-sarcolysin alone. The difference between melphalan on one hand, and m-L-sarcolysin and peptichemio on the other hand, may reflect a more rapid uptake of the latter substances. Inhibition of 3H-uridine incorporation in human peripheral lymphocytes supports this hypothesis. The frequency of sister chromatid exchanges in human fibroblasts was significantly higher after treatment with m-L-sarcolysin compared to melphalan, a finding which also indicates that these chemically closely related substances modify the cellular DNA differently. When DNA repair synthesis was induced by UV light and methyl-methane-sulfonate (a monofunctional alkylating agent), no additional DNA repair synthesis was induced, if peptichemio, m-L-sarcolysin or melphalan was added. These results indicate that the repair of lesions induced by melphalan peptichemio, UV-light and methyl-methane-sulfonate is mediated by at least one common controlling enzyme. (Author abstract) (17 Refs)

82. THE DECISION-POINT APPROACH FOR SYSTEMATIC CARCINOGEN TESTING.

Weisburger JH, Williams GM
Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Food Cosmet Toxicol; 19(5):561-566 1981

The decision-point approach provides a framework, based on current concepts of the mechanisms of carcinogenesis, for systematic evaluation of potential mutagenic and carcinogenic hazards of chemicals. Chemical carcinogens have been divided into two main categories-genotoxic agents, which interact with DNA and genetic material and lead to irreversible alterations in DNA, and epigenetic agents, which operate by distinct non-genotoxic mechanisms and are tissue-specific. Genotoxic agents include direct-acting carcinogens, procarcinogens, and inorganic carcinogens; the first two classes damage DNA either through direct chemical reactivity or following metabolism by enzyme systems, whereas inorganic carcinogens are not directly genotoxic but lead to changes in DNA by selective alteration in the fidelity of DNA replication. Epigenetic agents include solid-stage carcinogens, hormones, immunosuppressors, co-carcinogens, and promoters. The decision-point approach involves five steps: (1) consideration of the structure of the chemical; (2) in vitro short-term tests (mutagenesis, DNA repair, chromosome effects, and cell transformation); (3) limited in vivo bioassays (skin-tumor induction in mice, pulmonary-tumor induction in mice, breast-cancer induction in rats, induction of rodent liver altered foci, and assays for promoters); (4) chronic bioassay; and (5) final classification of a chemical as a genotoxic or epigenetic carcinogen. Health-risk analysis also must consider quantitative potential as well as qualitative positive or negative results. The proposed testing approach provides for systematic yet economical testing, the results of which can be applied to flexible, rational health-risk analysis. (26 Refs)

83. SIMULTANEOUS EXAMINATION OF SISTER CHROMATID EXCHANGES AND CELL REPLICATION KINETICS IN TUMOR AND NORMAL CELLS IN VIVO.

Schneider EL, Nakanishi Y, Lewis J, Sternberg H
Section Cellular Aging and Genetics, Lab. Cellular and Molecular Biology, Gerontology Res. Center, Natl. Inst. Aging, NIH, Baltimore, MD, 21224
Cancer Res; 41(12):4973-4975 1981

The bromodeoxyuridine differential chromatid labeling techniques were applied to the simultaneous in vivo examination of cell cycle kinetics and sister chromatid exchange (SCE) induction by various cancer chemotherapeutic agents in normal and Ehrlich ascites tumor cell populations. Compounds which yielded high ratios of SCE (in tumor cells):SCE (in normal cells) also produced greater inhibition of cellular replication in tumor cells when compared to normal cells. Thus, this approach permits in vivo assessment of induction of DNA damage by SCE analysis as well as inhibition of cellular replication by specific cancer chemotherapeutic agents in tumor and normal cell populations. (Author abstract) (21 Refs)

84. DIFFERENTIAL CHROMATID DAMAGE INDUCED BY 6-THIOGUANINE IN CHO CELLS.

Maybaum J, Mandel HG
Dept. Pharmacology, George Washington Univ. Medical Center, Washington, DC, 20037
Exp Cell Res; 135(2):465-468 1981

Treatment of Chinese hamster ovary cells with 6-thioguanine (TG) produces severely disrupted chromatin in G2 cells, as visualized with premature chromosome condensation. In many regions of the chromosome this damage, appearing as a gapped or diffusely staining region, occurs in only one of the sister chromatids. This morphology strongly supports previous reports that TG-induced cytotoxicity is related to its incorporation into DNA and that this lesion is expressed in the cell cycle following that in which drug exposure occurs. (Author abstract) (15 Refs)

85. DIFFERENTIAL INDUCIBILITY OF CHROMOSOME ABERRATIONS AND SISTER-CHROMATID EXCHANGES BY INDIRECT MUTAGENS IN VARIOUS MAMMALIAN CELL LINES.

Ikeuchi T, Sasaki M
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Mutat Res; 90(2):149-161 1981

A variety of mammalian cell cultures were examined for inducibility of chromosomal aberrations (CA) and sister chromatid exchanges (SCE) by the indirect mutagens cyclophosphamide (CP), dimethylnitrosamine (DMN), and benzo(a)pyrene (BP). Sixteen cell lines were examined for response to CP. All rat ascites hepatoma cell lines showed a significant increase in frequencies of both SCE and CA in a dose-dependent manner. Several rat esophageal tumor cell lines showed an extremely high sensitivity to CP, with significant yields of SCE and CA obtained at much lower concentrations compared to other cell lines. Seven cell lines were examined for their responsiveness to DMN. AH66-B, R1 and R3 cells, which showed a significant response to CP, were also sensitive to DMN in induction of CA. SCE frequency increased only slightly, however. Of the four cell lines studied for BP sensitivity, GHE cells showed the highest response to BP; frequencies of both SCE and CA were increased up to 3.8-and 6.9x. AH66-B and B-13 were moderately sensitive. HE2144 was almost insensitive but showed slightly increased frequency of SCE. (28 Refs)

86. EFFECT OF RETINOIDS ON PLATING EFFICIENCY, SISTER-CHROMATID EXCHANGE (SCE) AND MITOMYCIN-C-INDUCED SCE IN CULTURED CHINESE HAMSTER CELLS.

Sirianni SR, Chen HH, Huang CC
Dept. Biology, Niagara Univ., Niagara, NY, 14109
Mutat Res; 90(2):175-182 1981

Cytogenetic effects of five retinoids, all-trans-retinol (ROL), all-trans-retinoic acid (RA), all-trans-retinal (RAL), all-trans-retinyl acetate (RAc), and Ro. 10-9359 TMMP ethyl retinoate (TMMP), on cultured Chinese hamster cell line V79 were investigated. The five retinoids differed in ability to decrease plating efficiency. None induced sister-chromatid exchange

(SCE) and none had an effect on mitomycin-C-induced SCE. RAL was the most potent reducer of plating efficiency, followed in decreasing order by ROL, RAc, RA and TMMP. The results discount a cellular mechanism of retinoids based on mitotic recombination. (27 Refs)

87. RELATIONSHIP BETWEEN IN VIVO MITOMYCIN C EXPOSURE, SISTER CHROMATID EXCHANGE INDUCTION AND IN VITRO MITOGENIC PROLIFERATION. II. EFFECT OF AGING ON SPLEEN CELL MITOGENESIS AND SISTER CHROMATID EXCHANGE INDUCTION.

Mann PL, Kern DE, Kram D, Schneider EL
Oncology Center, Johns Hopkins Univ. Medical Center, Room1-127, Baltimore, MD, 21205
Mech Ageing Dev; 17(2):203-209 1981

In vivo administration of mitomycin C (MMC) produces an increase in both the frequencies of sister chromatid exchange (SCE) as well as inhibition of in vitro mitogenic responses. At low concentrations of MMC (2 mg/kg) spleen cell suspensions from both young and old mice showed similar patterns of mitogen inhibition and increased SCE frequencies. At high MMC concentrations (5 mg/kg) significant differences between young and old responses were observed. Spleen cells from young animals displayed mitogen-inhibition curves which plateaued with increasing doses of MMC, while the cells from old animals displayed a continuing increase in mitogenic inhibition. MMC-induced SCE frequencies revealed a complementary pattern: increasing SCE frequencies as a function of MMC concentration in young spleen cells while SCE levels plateaued in old spleen cell populations. The results of these studies suggest (1) that an inverse relationship exists between sister chromatid exchange induction and mitogenic response, (2) that cells from older animals may have an increased sensitivity to high levels of DNA damage (5 mg/kg MMC), and (3) that this sensitivity may be expressed functionally by increased inhibition of in vitro mitogenic responses. (Author abstract) (18 Refs)

88. METHYL METHANE-SULPHONATE (MMS) INDUCED SCES ARE REDUCED BY THE BRDU USED TO VISUALISE THEM.

Ockey CH
Paterson Lab., Christie Hosp., Holt Radium Inst., Withington, Manchester M 209 BX, England
Chromosoma; 84(2):243-256 1981

SCE induction in synchronized CHO cells treated with methyl methane sulfonate (MMS) in G1 was studied over successive pairs of cell cycles by introducing bromodeoxyuridine (BrdU) at consecutive G1 stages. When individual cell cycle SCE values were calculated from the data, anomalous results were obtained with ratios of 1.0:1.8:2.1 for the first three cycles but a negative value for the fourth cycle. Further studies using different BrdU concentrations showed that MMS induced SCEs were reduced by values exceeding 50% in DNA containing high levels of incorporated BrdU. This reduction was dose dependent and accounted for the anomalous results obtained over successive cycles. Lesions leading to chromatid exchanges were also reduced by the same mechanism. SCEs induced by UV irradiation were also decreased but those induced by the cross-linking agent nitrogen mustard (HN2) remained unaffected. The results indicate that not only are SCE lesions induced by MMS, UV or HN2 expressed independently of the 'spontaneous' SCEs induced by BrdU but that SCE lesions are multiple in nature. Mechanisms by which SCE lesions could be repaired in BrdU containing DNA are discussed. SCE lesions in MMS treated cells arrested in G1 with arginine deprived medium (ADM) are repaired without the presence of BrdU in the DNA. An opposite effect is seen however in the control cells, where SCEs are increased with time spent in ADM arrest. These interactions between the effects of MMS, BrdU and ADM arrest are discussed. (Author abstract) (14 Refs)

89. CONTRIBUTION OF INCORPORATED 5-BROMODEOXYURIDINE IN DNA TO THE FREQUENCIES OF SISTER-CHROMATID EXCHANGES INDUCED BY INHIBITORS OF POLY-(ADP-RIBOSE)-POLYMERASE.

Natarajan AT, Csukas I, Van Zeeland AA
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Mutat Res; 84(1):125-132 1981

The role of 5-bromodeoxyuridine (BrdUrd) incorporated into DNA on sister-chromatid exchanges (SCE) induced by inhibitors of poly-(ADP-ribose)-polymerase (PARP) was studied in Chinese hamster ovary (CHO) cells. Cells were grown in medium containing 5 uM BrdUrd to produce sister chromatids containing bifiliarly (BB) or unifiliarly (TB) substituted DNA. Other cultures were exposed to BrdUrd followed by thymidine (TdR) to produce unifiliarly substituted (TB) or unsubstituted (TT) DNA. Exposure to 3-aminobenzamide (3-AB: 0-10 uM) induced SCE in a dose-dependent manner (6.45-54.10 SCE/cell). Benzamide (BA) also produced dose-dependent SCE. Frequencies of SCE were doubled when 3-AB was present during the first cell cycle; the increase was six-fold when 3-AB was present during the second cell cycle. The increase was additive when 3-AB was present during both cycles. The DNA template used for replication, but not the presence of TdR or BrdUrd in the medium, was critical for induction of SCE. Both 3-AB and BA inhibited PARP. Results after reversal of DNA labeling patterns indicated that the presence of BrdUrd, rather than cell cycle number, was directly related to SCE. Mutations to HGPRT- were not increased by 3-AB or BA. Since 3-AB and BA produced SCE, but not point mutations, the SCE test may produce false positive results in mutagenicity tests. (13 Refs)

GENERAL REVIEWS

90. THE REPAIR OF DNA DAMAGE: RECENT DEVELOPMENTS AND NEW INSIGHTS.

Friedberg EC, Bonura T, Love JD, McMillan S, Radany EH, Schultz RA
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J Supramol Struct Cell Biochem; 16(1):91-103 1981

Recent research into enzymatic repair of base damage to DNA is reviewed. Escherichia coli and its phages have been the most suitable model systems for this research. Seven distinct DNA glycosylases have been isolated from E coli. These glycosylases are specific for particular types of DNA damage and catalyze hydrolysis of the N-glycosylic bond between nitrogenous bases and the deoxyribose-phosphate backbone of the DNA molecule. Apurinic/aprymidine (AP) endonucleases effect incision of DNA sites from which damaged bases have been removed by the glycosylases. AP nucleases may vary in their substrate specificity and for the direction of operation (5' or 3' action). UV endonucleases (EN) have been isolated from E coli infected with M luteus and T4 phages. UV EN catalyze the removal of UV-induced pyrimidine dimers. UV EN of E coli consists of a complex of products from the uvrA, uvrB, and uvrC genes. At least the uvrA and uvrB proteins are inducible and normally exist in very small amounts. An inducible, apparently error-free DNA repair pathway has been reported in E coli that produces a reduction in mutation rates and increases survival after pre-exposure to very low levels of mutagenic alkylating agents. Preliminary evidence suggests that DNA repair systems found in E coli may have similar, possibly more complex counterparts in eukaryotic systems. (75 Refs)

91. BIOLOGICAL MONITORING OF EXPOSURE TO CARCINOGENS.

Vainio H, Sorsa M, Rantanen J, Hemminki K, Aitio A
Tyoterveyslaitos, 00290 Helsinki 29, Finland
Duodecim; 97(15):1141-1152 1981

The authors discuss the various theoretical and practical alternatives presently available for controlling occupational exposure to genotoxic substances and the tumors, deformities, congenital defects and fertility loss that can result. They also outline a threefold line of defense: (1) determination of the fact of exposure (detection of substance or its metabolites in organism, urine mutagenicity, protein and nucleic acid alkylation products); (2) detection of early biologic effects (chromosome alterations, sister chromatid exchange in lymphocytes, changes in sperm cell morphology, fetoproteins); (3) diagnosis and treatment of illnesses if preventive measures have not proved successful in individual cases. Most of the procedures described are still in the experimental stage, and individual differences cause variation both in the degree of exposure and sensitivity to the amount of exposure. (61 Refs) (In FIN)

92. GENITOURINARY CANCERS.

Qazi R
Rochester Univ. Sch. Medicine and Dentistry, Rochester, NY
Practical Cancer Chemotherapy. Rosenthal SN, and Bennett JM, ed. Garden City, NY, Medical Examination Publishing Co., 461 pp., 1981.

Malignancies of the kidney, bladder, prostate and testes are reviewed in detail. Adenocarcinomas of the kidney comprise about 3% of all malignancies in the United States. A recent report of a family with hereditary renal cell carcinoma provides the first example of a dominantly inherited chromosome aberration which causes a high risk of a specific human malignancy. Surgery is the only curative therapy for renal cell carcinoma, with a 5-yr-survival rate after radical nephrectomy of 60-76%., Bladder cancer accounts for about 4.5% of new cancers in the United States each yr, with transitional cell carcinomas accounting for 90% of the total. Optimal management of high grade invasive bladder cancer consists of radical cystectomy with preoperative radiation therapy. Nevertheless, greater than 50% of treated patients develop distant metastases within 2 yr and require systemic therapy. Because cis-platinum is the most effective single agent in bladder cancer, platinum-based combinations are being widely investigated. Adenocarcinoma of the prostate is the third most common cause of cancer death in males, following lung and colorectal cancers. Both surgery and radiation therapy with curative intent are used to treat localized carcinoma of the prostate. Testicular carcinoma accounts for only 1-2% of malignant tumors in males but represents the most common cause of cancer deaths in the 29-35 yr age group. Diagnosis, staging and treatment of the various histologic types of testicular tumors are discussed. (102 Refs)

93. EPIDEMIOLOGY OF CANCER IN CHILDHOOD.

Li FP, Bader JL
Sidney Farber Cancer Center, Boston, MA
Hematology of Infancy and Childhood Volume II. Nathan D Gand Oski FA, ed. Philadelphia, W. B. Saunders Company, 774 pp., 1981.

The incidence of malignant neoplasms in children less than 15 yr old in the United States is discussed. Of 7,168 new cases reported in 1970, leukemia was the most frequently occurring cancer (2,357) followed by tumors of the CNS (1417), lymphoma (787), neuroblastoma (540), soft tissue sarco ma (463), Wilms' tumor (450), bone tumor (323), retinoblastoma (197), liver tumor (100), ovarian tumor (77), testicular tumor (57), and others (400). Cancer risk factors discussed are the environmental carcinogens ionizing radiation, drugs, chemicals, and infectious agents. Host susceptibility includes single-gene diseases, chromosomal disorders, familial cancers, and cancer and birth defects. (288 Refs)

94. SOME GENETIC ASPECTS OF CANCER.

Bernstein R
Dept. Human Genetics, Sch. Pathology, Univ. Witwatersrand, Johannesburg, South Africa
S Afr Cancer Bull; 25(3):147-153 1981

Some of the genetic factors interacting with environmental mutagens in the etiology of cancer, are discussed under the headings of (1) inherent chromosome imbalance and (2) single gene mutations. These single gene disorders may be due to (a) defects in DNA replication and/or repair pathways causing cellular instability or (b) defects in immune surveillance mechanisms for protecting the cell. These genetic factors are correlated with the visible chromosomal markers of malignant or potentially malignant cells. (Author abstract) (38 Refs)

95. THE APPLICATION OF DNA RECOMBINANT TECHNOLOGY TO THE ANALYSIS OF THE HUMAN GENOME AND GENETIC DISEASE.

Davies KE
Biochemistry Dept., St. Mary's Hosp. Medical Sch., Univ. London, London W2 1PG, England
Hum Genet; 58(4):351-357 1981

Application of recombinant DNA techniques to analysis of genetic disease at the genome level is reviewed. Chromosomal rearrangements associated with neoplasia are discussed; DNA recombinant technology may prove a useful tool in the dissection of events leading to neoplasia. (69 Refs)

96. ACUTE LEUKAEMIA, PERSPECTIVES IN DIAGNOSIS AND TREATMENT.

Zwaan FE, Jansen J
Dept. Internal Medicine, Univ. Hosp., Rijnsburgerweg 10, 2333 AA Leiden, Netherlands
Neth J Med; 24(5):190-194 1981

Perspectives in diagnosis and treatment of acute leukemia are reviewed. Advances in cytochemical, immunologic, cytogenetic, and in vitro culture methods allow most centers to identify the neoplastic cell involved in any individual case. One method is the FAB classification for acute non-lymphocytic leukemia (ANLL), based on morphologic features and cytochemical reactions. Antigens detectable by immunofluorescence methods are useful for distinguishing subtypes of acute lymphocytic leukemia (ALL). Presence of the 'common ALL' antigen is correlated with good prognosis, whereas markers for T- and B-cells (sheep RBC receptors) usually indicate poor prognosis. New markers holding promise for differentiation of ALL subtypes include terminal deoxynucleotidyl transferase and the Ia-like antigens. Techniques for culturing normal progenitor cells have aided in the prediction of leukemic relapse; recent development of techniques for culturing leukemic progenitor cells may aid in selecting cytotoxic chemotherapeutic agents. Discovery of the Philadelphia chromosome and other translocations may be useful in cytogenetic diagnosis and determination of prognosis. Excellent results in the treatment of childhood ALL have been achieved with protocols based on 'total therapy,' which include remission induction chemotherapy, CNS prophylaxis with cerebral irradiation, and maintenance chemotherapy. ANLL has a poor prognosis, but modified supportive care has improved therapeutic results. Allogeneic bone marrow transplantation has been of limited success in acute myeloid leukemia. New techniques for prevention or suppression of immunologic interaction between donor and recipient must be evaluated. (26 Refs)

97. CHRONIC MYELOID LEUKEMIA (A STATE OF THE ART REPORT).

Chrobak L
I. Vnitrni klinika fakulty, Universita Karlova, 500 36 Hradec Kralove, Czechoslovakia
Vnitr Lek; 27(9):899-904 1981

Chronic myeloid leukemia (CML) is a clonal disease due to an affection of the pluripotent Philadelphia chromosome-positive and -negative stem cells. The clonal origin of CML is demonstrated by the study of the glucose-6-phosphate dehydrogenase isoenzymes. The significance of the Philadelphia chromosome in the origin of the pathological clone is still unclear, and it cannot be ruled out that it represents a secondary phenomenon. The disease develops in two phases: the chronic phase, usually with a favorable response to treatment, and an accelerated phase, ending in blastic conversion in the majority of the cases, which conversion is heralded sometimes by changes in the behavior of granulocyte colonies in vitro. Besides myeloblastic conversion, lymphoblastic conversion with a favorable response to vincristine and prednisone occurs in almost 30% of all cases. The increasing incidence of meningeal affections is due to the increasing remission rate. Busulfan continues to be used in the treatment during the chronic phase of CML. Splenectomy during the early phase of the disease proved to be ineffective. (69 Refs) (In CZE)

98. CHRONIC MYELOID LEUKAEMIA.

Woodruff RK
Dept. Haematology, Austin Hosp., Heidelberg, Victoria 3084, Australia
Aust NZ J Med; 11(6):678-686 1981

The etiology of chronic myeloid leukemia (CML) and management of the chronic and blastic transformation (BM) phases are reviewed. Brief consideration is given to Philadelphia (Ph1) chromosome positive cases of acute leukemia. Except for exposure to high level (atom bomb) radiation, etiology of CML remains obscure. The clinical and hematological features of the chronic phase, cytogenetics, and prognostic features are discussed. Busulfan is the standard drug in treatment, although other drugs appear equally effective. Use of intensive leucopheresis in the initial phase of disease can produce improvement which can only be maintained with simultaneous cytotoxic chemotherapy. A modest increase in survival in one trial was attributed to immunotherapy using BCG and tumor cells from patients with acute myeloblastic leukemia maintained in tissue culture. Intensive chemotherapy in attempts to eradicate the Ph1 positive clone has been accompanied by significant morbidity and toxicity; no evidence exists that reduction in the proportion of Ph1-positive cells results in better survival. Bone marrow transplantation from identical twins was beneficial in four chronic phase patients following treatment with chemotherapy and irradiation. Treatment of BT also involves chemotherapy but may be accompanied by an increased risk of meningeal leukemia. Autologous bone marrow reconstitution is feasible and may prevent life-threatening complications in the acute phase. Syngeneic and allogeneic bone marrow transplantation have also been employed. Future directions are discussed. (105 Refs)

99. CYTOGENETICS.

Gerald PS
Dept. of Pediatrics, Harvard Medical Sch., Boston, MA
Hematology of Infancy and Childhood Volume II. Nathan D Gand Oski FA, ed. Philadelphia, W. B. Saunders Company, 774 pp., 1981.

Background information is provided on the genetic study of the hematopoietic system and its various disorders. The use of phytohemagglutinin to stimulate mitosis, staining techniques for identification of chromosome pairs and for recognizing differences in DNA synthesis, and cytogenetic aspects of hematologic disorders are among topics discussed. (41 Refs)

100. IMPORTANCE OF CYTOGENETIC ALTERATIONS IN NEOPLASTIC TRANSFORMATION IN LYMPHOMAS.

Slavutsky IR
Instituto de Investigaciones Hematologicas, Academia Nacional de Medicina, Pacheco de Melo 3081, 1425 Buenos Aires, Argentina
Medicina (B Aires); 41(3):382-385 1981

This general overview of lymphomas' cytogenetic studies stresses importance and specificity of 14q+ marker with its 50% frequency in lymphomas (L), t(8q-;14q+) characteristic of Burkitt lymphoma and t(11q-; 14q+) of lymphosarcoma. L could be characterized according to 14q+ translocations or to different markers detected. Correlation between cytogenetic examination and clinical staging should be established. Cytogenetic studies should contribute to the clarification of histological classification and therapy response. (no Refs) (In SPA)

101. MULTIPARAMETER FLOW CYTOMETRY. PART I: APPLICATION IN ANALYSIS OF THE CELL CYCLE.

Darzynkiewicz Z, Andreef M
Sloan-Kettering Inst., New York, NY
Clin Bull; 11(2):47-57 1981

Application of multiparameter flow cytometry to study of the cell cycle is reviewed. Techniques designed to measure other cell features in addition to DNA content are specific for RNA content and simultaneous DNA and RNA content, detection of incorporated 5-bromodeoxyuridine, and analysis of nuclear chromatin structure. (56 Refs)

OTHER RELATED STUDIES

102. CORRELATIONS BETWEEN SISTER CHROMATID EXCHANGE FREQUENCIES AND REPLICON SIZES: A MODEL FOR THE MECHANISM OF SCE PRODUCTION.

Cleaver JE
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Exp Cell Res; 136(1):27-30 1981

Baseline sister chromatid exchanges (SCEs) increase as a function of av replicon size in a variety of human and Chinese hamster cell lines. This observation is the basis for a model in which SCEs are generated by errors in the unravelling of daughter double helices by topo isomerases. These errors cause exchanges behind the replication fork, not at the fork as several current models assume. This model also provides an explanation for SCEs induced when residual DNA damage that has been replicated interferes with the normal processes of unravelling the daughter strands. (Author abstract) (26 Refs)

103. PRELIMINARY STUDY OF G BANDING OF CHROMOSOMES WITH LOCAL MADE TRYPSIN.

Yan J
Dept. Pediatrics, First Affiliated Hosp., Wuhan Medical Coll., Wuhan, People's Repubic of China
Zhonghua Yixue Jianyan Zazhi; 4(1):37-38 1981

Use of locally made trypsin in G banding of chromosomes is described. When this method was applied to the study of the Philadelphia chromosome of a chronic granulocytic leukemic patient, not only deletion of the long arm of chromosome 22 was observed, but also the translocation of this deleted arm to the long arm of chromosome 9. It was concluded that the banding technic using locally made trypsin is rapid, stable, simple and requires no special equipment. (7 Refs) (In CHI)

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CLINICAL STUDIES OF CHROMOSOMES IN HUMAN CANCER

1. SPECIFIC CHROMOSOME DEFECT ASSOCIATED WITH HUMAN SMALL-CELL LUNG CANCER: DELETION 3P(14-23).

Whang-Peng J, Kao-Shan CS, Lee EC, Bunn PA, Carney DN, Gazdar AF, Minna JD
Medicine Branch, Div. Cancer Treatment, NCI, NIH, Bethesda, MD, 20205
Science; 214(4529):181-182 1981

A specific, acquired chromosomal abnormality (deletion 3p) has been found in at least one chromosome 3 in 100% of the

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metaphases in 12 of 12 cell lines cultured from human small-cell lung cancer tissue and in 2-day tumor culture specimens from three patients. Analysis of the shortest region of overlap shows the deletion to be 3p(14-23). This specific change was not seen in five of five lung cancer cell lines other than small-cell lung cancer or in two lymphoblastoid lines cultured from cells of small-cell lung cancer patients whose tumors had the 3p deletion. (Author abstract) (11 Refs)

2. A CASE OF SEZARY SYNDROME.

Takubo T, Namiuchi S, Ueda T, Shibata H, Nakamura H, Masaoka T, Yoshitake J, Saheki O, Maeda S
Dept. Internal Medicine, Center for Adult Diseases, Osaka, Japan
Nippon Gan Chiryo Gakkai Shi; 16(4):694-703 1981

A 47-yr-old man, who presented with fever of 38 C, fatigue, wt loss, and history of a transient, systemic skin rash, was diagnosed as having Sezary syndrome. The clinical, cytomorphological, and immunochemical findings are described. Characteristics observed included T cell type, skin infiltration, little infiltration into bone marrow, typical cellular morphology, high T-mu value with suppressor function, chromosomal aberration, and trisomy of chromosomes 8 and 16. (10 Refs)

3. MONOSOMY 7 IN CHILDHOOD: A PRELEUKAEMIC STATE (MEETING ABSTRACT).

Chessells JM, Sieff CA, Pickthall HJ, Lawler SD
Departments of Haematology and Immunology, Hospital for Sick Children and Institue of Child Health, London, England
Br J Haematol; 49(1):129 1981

Between 1976 and 1979 Monosomy 7 was diagnosed in six boys aged 5 1/2 mo to 8 yr. Presenting features included hepatosplenomegaly (5/6), respiratory infections (4/6), pallor (2/6) and skin infections (1/6). Hematological features included a leukoerythroblastic anemia with leukocytosis and thrombocytopenia, and a hyperplastic marrow with a slight excess of blasts. Fetal Hb was normal or mildly raised (2/6), neutrophil function tests showed defective chemotaxis with reduced kiling, despite a normal nitroblue tetrazolium test. Cytogenic analysis of the marrow showed a preponderence of cells with Monosomy 7; the blood lymphocytes were normal. In three patients disease progressed to acute myeloid leukemia (AML) after 3 wk to 23 mo; the only patient who remitted received 6-mercaptopurine and prednisolone, but relapsed 16 mo later. A fourth child died from anemia and respiratory infection and a fifth developed massive splenomegaly and terminal myelofibrosis. The sixth patient is still in a stable state. Monosomy 7 is one of the commoner myeloproliferative states in childhood and carries a high risk of progressing to AML. The acute phase is usually resistant to chemotherapy, but even if responsive, treatment does not result in elimination of the abnormal clone. Allogeneic bone marrow transplantation should be considered in cases with a suitable donor. (no Refs)

4. 12. TREATMENT OF ACUTE LEUKEMIA IN REMISSION BY BONE MARROW TRANSPLANTATION.

Storb R
Div. Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Recent Results Cancer Res; 80:73-77 1982

Before 1975 only patients with chemotherapy-refractory acute leukemia were treated by marrow transplantation. The preparative regimen developed in Seattle consisted of cyclophosphamide followed 2-3 days later by 1,000 rad total body irradiation from two opposing cobalt sources and a marrow transplant from an HLA-identical sibling. Of the first 100 patients, 13 were alive in unmaintained remission 5.5-10 yr after transplantation with functioning marrow grafts. In this initial series of patients leukemic recurrence was one of the major problems. Attempts to reduce recurrent leukemia by the use of more aggressive antileukemic regimens before transplantation were unsuccessful. In early 1976 a study of acute leukemia patients transplanted in remission was begun. Twenty-two patients with acute lymphoblastic leukemia were transplanted in second, third, or subsequent remission and 8 (35%) are now in unmaintained remission 2.5-4.5 yr later. Recurrent leukemia was the cause of death for 11 patients in the acute lymphoblastic leukemia group. Twelve of the first 19 patients with acute nonlymphoblastic leukemia grafted in first remission are now alive and well in unmaintained remission 2-4 yr after transplantation. At present 48 patients have been included in the study and 31 (65%) are living in remission. Only one of the 48 patients has had a recurrence of leukemia. The principal causes of death were graft-versus-host disease and interstitial pneumonia. Marrow transplantation for patients with chronic myelogenous leukemia in blast crisis had resulted in one unmaintained remission surviving now, at 4.5 yr, among six patients with syngeneic grafts and four long-term survivors (8, 15, 27, and 31 mo) among 22 patients with allogeneic grafts. Three of four patients with chronic myelogenous leukemia in chronic phase given syngeneic transplants are now in remission with lack of Philadelphia chromosome at 3-4 yr, while one had reappearance of the Philadelphia chromosome at 2.5 yr and is now surviving in the chronic phase. (Author abstract) (11 Refs)

5. IN VIVO AND IN VITRO ACTIVITY OF NEUTROPHIL ALKALINE PHOSPHATASE IN ACUTE MYELOCYTE LEUKEMIA WITH 8;21 TRANSLOCATION.

Kamada N, Dohy H, Okada K, Oguma N, Kuramoto A, Tanaka K, Uchino H

Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., 1-2-3 Kasumi-cho, Minami-ku, Hiroshima 734, Japan

Blood; 58(6):1213-1217 1981

Cytogenetic studies were made on 160 patients with acute nonlymphocytic leukemia (ANLL) between 1963 and 1979, of whom 115 had acute myelocytic leukemia with 67 patients showing aneuploidy (58.3%). Among these, 24 patients were found to have similar chromosome alterations that appeared to involve specifically chromosomes 8 and 21. Banding studies on at least seven of these patients confirmed the presence of a translocation between these two chromosomes. Of 160 ANLL patients, 142 were scored for neutrophil alkaline phosphatase (neutrophil AP) at the time of diagnosis. Fifty-nine patients showed a low neutrophil AP score, 42 a normal value, and 41 a high value. All patients with 8;21 (or C/G) translocation had a low neutrophil AP score and leukemic cells with maturation (M2 of FAB classification) in the bone marrow. In vitro liquid culture for 2 wk of 8;21 translocated leukemic cells revealed no increase of neutrophil AP activity nor increase of mature granulocytes, whereas 9;22 translocated chronic myelocytic leukemia cells with a low neutrophil AP score did so. Neutrophil AP score at the time of diagnosis in acute myelocytic leukemia is very useful for detecting 8;21 translocation AML and for studying the pathophysiology and genetic alterations of the characteristic subgroup of AML with 8;21 translocation. (Author abstract) (23 Refs)

6. THE CLINICAL SIGNIFICANCE OF ATYPICAL PH1 CHROMOSOMES IN CHRONIC GRANULOCYTIC LEUKAEMIA (MEETING ABSTRACT).

Watmore AE, Potter AM, Cooke P, Lilleyman JS, Sokol RJ
Departments of Human Genetics and Haematology, Sheffield Children's Hospital, Sheffield, England
Br J Radiol; 56(644):140 1981

One hundred and nineteen unselected and similary treated patients with Ph1 positive chronic granulocytic leukemia (CGL) had the precise nature of their chromosome rearrangements producing the Ph1 studied to determine whether this had any clinical relevance. Twenty (17%) did not have the usual 9/22 translocation, and these, by life table analysis, had a significantly shorter benign phase of their disease than the others. It further appeared that possession of an atypical Ph1 related to age in that only 24 patients were over 60 at diagnosis but nine (38%) had a non-9/22 variant. As age itself also appeared to influence the duration of the benign phase, irrespective of Ph1 type, the question arose whether atypical Ph1 chromosomes were thus simply occurring in older patients or whether they were affecting prognosis independently. Despite relatively small numbers, it was evident that the 11 patients who had a non-9/22 Ph1, and who were under 60, had significantly shorter benign phase than the 84 of similar age with a typical Ph1. It is suggested that myeloid karyotype in the benign phase of CGL can provide information on prognosis. (no Refs)

7. CHRONIC MYELOGENOUS LEUKAEMIA IN INFANCY AND CHILDHOOD: A 10-YEAR STUDY AT NEW DELHI, INDIA.

Rani S, Beohar PC, Mohanty TK, Gupta S
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Acta Haematol (Basel); 66(4):233-237 1981

Chronic myelogenous leukemia (CML) rarely occurs in children. This study, the only Indian one in which Philadelphia (Ph') chromosome was studied, lasted over 10 yr and comprises 7 cases of CML out of 88 leukemias in infancy and childhood. In five of these seven cases, Ph' chromosome was studied and was found to be negative in all five. The Indian and the Western literature is reviewed and the rarity of the disease emphasized along with the higher incidence among Indian children, compared to the West. (Author abstract) (18 Refs)

8. UNUSUAL CHROMOSOMAL TRANSLOCATION, T(1P+,7Q-), AND FAMILIAL LEUKEMIA IN A PATIENT WITH CHRONIC MYELOMONOCYTIC LEUKEMIA.

Roush GC
Connecticut Cancer Epidemiology Unit, Yale Univ., 135 Coll. St., New Haven, CT, 06510
Conn Med; 45(12):767-771 1981

A single case of chronic myelomonocytic leukemia (CMML) occurring in a 68-yr-old man with an unusual chromosomal translocation t(p+,7q-) and a family history of adult leukemia is reported. Persistent monocytosis in peripheral blood, proliferation of immature myelocytes in the marrow, and high serum and urine lysozymes led to the diagnosis of CMML. The observed translocation was evident in peripheral blood and marrow myeloid cells in the latter part of the patient's 8 yr course of disease. Two of the patient's cousins had chronic lymphocytic leukemia, a sister had acute undifferentiated leukemia, and a grandson had Hodgkin's disease. Since analysis occurred subsequent to busulfan treatment, the possibility exists that the abnormal karyotype was caused by the action of the alkylating agent. Translocations such as that reported here, however, have not been observed in other series of patients receiving busulfan. (47 Refs)

9. 13. PREVENTION OF BLASTIC CRISIS IN PH(1)-POSITIVE CHRONIC MYELOID LEUKEMIA.

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Dept. Hematology, King's Coll. Hosp., Denmark Hill, London SE5 9RS, England
Recent Results Cancer Res; 80:78-82 1982

Fourteen untreated patients with Ph(1)-positive chronic myeloid leukemia received combination chemotherapy consisting of blocks of doxorubicin, vincristine, cytosine arabinoside and 6-thioguanine. Significant karyotypic conversion occurred in sick patients, the percentage of Ph(1)-positive cells in the bone marrow falling by at least 50%. Maintenance therapy comprised vincristine, busulfan hydroxyurea, 6-mercaptopurine and dibromannitol in rotation. Reinduction therapy was administered when Ph1 positivity reverted to 100%. Karyotypic reconversion was achieved in three of four patients. After induction, chromosome analysis of the bone marrow was performed every 3-6 mo to detect the appearance of aneuploid clones, the intention being to intensify therapy at that stage. (Author abstract) (10 Refs)

10. PROGNOSTIC VALUE OF SERIAL MEASUREMENTS OF LEUKOCYTE THYMIDINE UPTAKE IN WELL-CONTROLLED CHRONIC MYELOCYTIC LEUKEMIA.

Gomez GA, Herrmann R, Sokal JE
Dept. Medical Oncology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Leuk Res; 5(6):497-503 1981

Serial simultaneous determinations of uptakes of 3H-thymidine (3H-Tdr) by blood and marrow WBC in 29 patients (10 males, 19 females; 12-71 yr old) with well-controlled, Philadelphia chromosome-positive chronic myelocytic leukemia (CML) were examined for ability to provide early warning of disease progression from chronic to terminal stage. The 3H-TdR uptake values varied considerably from patient to patient (median values 0.9-18 disintegrations/min/10(3) WBC); these values were not, however, significantly different from those of controls. Also, the 3H-TdR uptake was not affected significantly by changes in the chemotherapy agents administered. Eleven patients (Group I) had a greater than four-fold increase in blood 3H-TdR between sequential determinations. Ten of the Group I patients entered the terminal phase of CML 2-6 mo after the increase in 3H-TdR uptake; 9/10 patients died 7-34 mo (median 10 mo) after the increase. One of the 18 patients (Group II) whose 3H-TdR did not increase died of ulcerative colitis, with CML under good control; 5 of the remaining 17 patients entered terminal phases 5, 6, 7, 8, and 12 mo after the last evaluable determination. The proportion of patients exhibiting disease progression was significantly less in Group II (28% within 1 yr; 11% within 6 mo) than in Group I. The marrow 3H-TdR did not show any consistent trend in either group and had no prognostic importance. Hematologic findings in blood and marrow at the time of 3H-TdR increase and at the time of the last previous evaluable study are presented. Chromosome analysis of the CML patients is described. The results indicated that periodic measurement of 3H-TdR uptake by circulating WBC may be useful for providing early warning of disease progression in the follow-up of patients with well-controlled CML. (15 Refs)

11. TWO CASES OF SECONDARY LEUKEMIA ACCOMPANIED BY CHROMOSOME ABNORMALITIES.

Taguchi H, Niiya K, Machida K, Takaoka M, Shiomi F, Ueda N, Shiraishi Y

Dept. Internal Medicine, Kochi Prefectural Central Hosp., Kochi, Japan

Rinsho Ketsueki; 22(7):1152-1159 1981

Two patients developed acute myelocytic leukemia after chemotherapy with or without radiotherapy was administered for primary cancers. One patient, a 56-yr-old man, was treated with combination chemotherapy [cyclophosphamide, (CPM), vincristine, (VCR), methotrexate; procarbazine] and radiotherapy (6,000 rads total) for primary lung cancer of the upper right lobe. Prior to treatment, peripheral blood and bone marrow were normal. A second course of radiotherapy (4,000 rads) was administered 5 mo after the first course when tumor shrinkage was observed with roentgenography. Three mo later, high fever and leukocytosis were observed, and acute myelocytic leukemia was diagnosed. Dicentric and ring chromosomes were observed in bone marrow cells at this time. The patient did not respond to combination chemotherapy [daunomycin, cytosine arabinoside, neocarzinostatin, VCR, prednisolone, (PRD)] and died. The other patient, a 49-yr -old man, was treated with combination chemotherapy (bleomycin; VCR; CPM; PRD) for diffuse-type malignant lymphoma; complete remission was achieved. Prior to therapy, peripheral blood and bone marrow showed no abnormalities, but acute myelocytic leukemia was diagnosed 3 mo after other chemotherapy was administered for relapse. Numerous hypodiploid cells were observed in the bone marrow cells. (17 Refs) (In JPN)

DNA CONTENT AND PLOIDY CHANGES ASSOCIATED WITH CANCER

12. FREQUENCY OF ANEUPLOID CELLS IN HUMAN SOLID TUMORS (MEETING ABSTRACT).

Frankfurt O, Slocum H, Greco W, Rustum Y

Roswell Park Memorial Institute, Buffalo, NY

VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

DNA histograms were obtained from cell suspensions of 70 surgically removed human solid tumors (lung, colon, sarcoma, melanoma and others). Samples were stained by two different (DNA) fluorochromes: propipidium iodide (PI) (after RNAse treatment) and DAPI [4',6-diamidino-2-phenylindole]. Blood WBC were used as a diploid standard. Aneuploid cells were found in nearly 60% of the tumors investigated and constituted between 10-90% of the cells in suspensions. Diploid cells were found in suspensions from 69 of the 70 tumors. Two aneuploid clones were found only in one tumor. Ploidy index varied from 1.1 to 2.7. The percentage of aneuploid cells in the majority of tumors was significantly higher in suspensions obtained by mechanical vs enzymatical methods. Ploidy indexes measured in the same tumor after staining with PI and DAPI were highly correlated. This indicates that flow cytometric measurement of ploidy reflects DNA content, rather than DNA stainability. (2 Refs)

13. CLONOGENIC ASSAY AND OTHER PARAMETER MEASUREMENTS OF CELLS FROM HUMAN LUNG CARCINOMA AND OTHER SOLID TUMORS (MEETING ABSTRACT).

Slocum HK, Pavelic ZP, Frankfurt O, Wake N, Sandberg AA, Greco WR, Rustum YM

Roswell Park Memorial Institute, Buffalo, NY, 14263

Third NCI-EORTC Symposium on New Drugs in Cancer Therapy, October 15-17, 1981, Brussels, Belgium European Organization for Research on Treatment of Cancer; :A23 1981

Mechanical disaggregation of human solid tumors leaves substantial numbers of cells undisaggregated, which are available by subsequent enzymatic treatment. We have compared trypan blue exclusion, ribonucleoside triphosphate pool sizes, clonogenicity and drug sensitivity in semisolid media, karyology, and DNA content by flow cytometry of cells obtained mechanically and enzymatically. Cells released in the mechanical step were generally unable to exclude trypan blue, displayed depleted ribonucleoside triphosphate pools, and seldom were useful for determination of karyotype. Flow cytometry indicated the presence of aneuploid cells in mechanically derived suspensions from 80% of lung, colorectal, and breast carcinoma specimens, and greater than 50% of specimens of melanoma, sarcoma, and ovarian, renal, and bladder carcinoma. High probability of dye exclusion, and higher ribonucleoside triphosphate pools were characteristic of cells released in the enzymatic step. Forty-one of 51 samples (80%) were successfully karyotyped with enzymatically obtained cells, with 10 of these revealing normal diploid karyotype. Flow cytometry revealed that large aneuploid populations present in mechanically derived suspensions were often markedly reduced in enzymatically derived suspensions from the same specimen. Treatment of mechanically derived cells with the enzyme mixture generally eliminated most trypan blue admitting cells, and resulted in reduction of the aneuploid population. Comparing the clonogenicity and drug sensitivity in soft agar of mechanically and ezymatic derived cells, in 44 cases we have found no significant differences. (no Refs)

14. DNA MEASUREMENTS BY SINGLE NUCLEI FLOW CYTOMETRY IN HUMAN ACTINIC SKIN LESIONS.

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J Invest Dermatol; 77(6):431-433 1981

A basal cell carcinoma, a Bowenoid carcinoma and clinically normal nonexposed skin from a 76-yr-old male with numerous epidermal tumors on sun-damaged skin were investigated by DNA flow cytometry and the results were compared with data obtained from normal skin of a control group. From each type of skin lesion three different biopsies were examined. Each of the DNA frequency distribution histograms showed bimodal configuration revealing no more than one DNA stem line, which was diploid in the unaffected skin and the Bowen carcinoma and hyperdiploid in the basal cell carcinoma. The three different types of skin could be clearly separated by means of at least one of three parameters: S-fraction, G2 + M fraction or S/G2 + M index. The S/G2 + M index came out as the most sensitive discriminator for the tumors. The S-fraction level was higher in the clinically normal skin of the investigated male than in the control group and further high in the tumors. (Author abstract) (15 Refs)

15. COMPARISON OF STEROID RECEPTOR CONTENT AND DNA LEVELS IN HUMAN BREAST CANCERS (MEETING ABSTRACT).

Thornthwaite JT, Coulson PB
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VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Slona-Kettering Cancer Center; 1981

The purpose of this study was to determine if there is any correlation between the degree of heteroploidy in human breast cancers and the quantity of steroid receptors in these tissues. Fro zen specimens (-85 C) with estrogen cytosolic receptor levels between 0-502 fm/mg cytosolic protein were prepared for DNA flow cytometric analysis. This was accomplished by mincing the tissues in a special nuclear isolation medium (NIM) containing 10 ug/ml of 4',6-diamindino-2 phenylindole-2HCl (DAPI) at room temperature. The isolated nuclei were filtered (70 micron mesh) and syringed to assure a monodispersed nuclear population. A modified PHYWE ICP-21 flow cytometer, either with the PHYWE flow chamber for DNA or the Cell Technology transducer for dual parameter analysis (electronic nuclear vol vs DNA fluorescence) was utilized. The range of CVs of the G1/0 peaks of NIM-DAPI prepared tissues were routinely 1-3%. Samples were grouped according to their DNA contents and designated diploid-like, diploid/hypodiploid, diploid/hyperdiploid, diploid/multiploid, or diploid/hypertetraploid. No correlation could be seen between the percentage of hyperdiploid cells or the proliferation index compared to the estrogen (3H-estradiol), progesteron (3H-R5020) or, testosterone (3H-R1881) receptor levels. In 84 tumors, the percentage of breast cancers which were diploid or aneuploid were 30% or 70%, respectively. Work is in progress to see if there is any correlation between the degree of aneuploidy and recurrence. (no Refs)

16. GENETIC AND CELL KINETIC CHARACTERIZATION OF MALIGNANT MELANOMAS BY FLOW CYTOMETRY (MEETING ABSTRACT).

Schumann J, Gonde W, Bruchmuller S, Straub C
University of Munster, 4400 Munster, W. Germany
VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

In 250 patients with malignant melanomas the DNA-distribution patterns of 95 primary tumors and of 316 metastasis were determined by flow cytometry using an ICP. Aneuploid cell lines could be identified in 82% of all patients, 72% of the aneuploid lines were in the tritetraploid range. Thirty-eight percent of the primary tumors showed more than one malignant cell line, they were multiclonal, whereas this rate in metastasis was below 10%. Ploidy was quanitified by DNA-Index (DNA-Index equals 2 stands for normal G1-cells with diploid DNA-content). The mean DNA-Index of all melanomas was 3.3. In melanomas with Clark's level II the mean DNA-Index was 3.5, with level III 3.3, with level IV 3.1 and with level V 2.9. The rate of aneuploidies was higher in level V (86%) than in level IV and III (each 80%) or level II (68%). Male patients had 88% aneuploidies with a mean-DNA-Index of 3.1, females 76% aneuploidies with a mean-DNA-Index of 3.4. The S-phase-fraction (mean 14.4%) was not correlated with certain ploidy stages but was a little bit higher in the triploid range than in the tetraploid range or the near diploid range. Tumors with higher S-phase fractions seem to be more sensitive to chemotherapy. In a number of patients different metastasis with genetical different cell lines could be detected at the same time. (no Refs)

17. MAMMALIAN SPERMATOGENESIS AS A BIOLOGIC DOSIMETER FOR RADIATION.

Hacker U, Schumann J, Gohde W, Muller K
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Acta Radiol Oncol Radiat Phys Biol; 20(4):279-282 1981

Mouse spermatogenesis was used as an in vivo test system obviously suitable as a biologic dosimeter. Ionizing irradiation induced changes in the frequency distribution of the cellular DNA content of whole testis preparations. These changes can be analyzed by flow cytometry. Such measurements deliver information on: (1) an increase of the coefficient of variation of the DNA histograms of some spermatogenic cells, (2) induction of diploid mature sperm, and (3) the dose-depending inactivation of the highly sensitive differentiated spermatogonia. In this model especially No 3 delivers quantitative information on the cytotoxic action of ionizing irradiation and chemical noxae as well, whereas Nos 1 and 2 may be used as qualitative criteria of mutagenic action of physical and chemical agents, No 2 obviously being more sensitive than No 1. (Author abstract) (17 Refs)

18. FLOWCYTOMETRY (FCM) OF HUMAN TESTICULAR TISSUE (MEETING ABSTRACT).

Pfitzer P, Gilbert P, Rolz G, Vyska K
No affiliation given
VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

FCM on testicular tissue of more than 100 autopsies showed differences in the proportion of substained spermatozoa, haploid spermatids, diploid 2C-nuclei and premeiotic spermatozoa in 4C-class. The evaluation of the histograms was performed computer-assisted and gave precise percentages of the different classes in the cell population. While healthy cases from accidents or forensic medicine furnished the control values cases of liver cirrhosis showed a nearly complete loss of the haploid class as consequence of the hormonal imbalance. Circulatory insufficiency resulted in an early break-down of spermatogenesis in cases of prolonged shock and to an irregular degree in cases of arteriosclerosis. Irregular reductions were also observed in cases of benign hyperplasia of the prostate. Cancer patients showed a loss of spermatogenesis in correlation to therapy and extent of disease. FCM therefore allows to measure the influence of different diseases on the sensitive system of male spermatogenesis by controlling the part of the various DNA-classes. With sufficient autoptical data the method may be applicable to the diagnoses of biopsies. (no Refs)

19. FLOW CYTOMETRIC ANALYSIS OF MAMMALIAN SPERM DEVELOPMENT AND DIFFERENTIATION (MEETING ABSTRACT).

Evenson DP, Claps ML, Darzynkiewicz Z, Melamed MR
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

Flow cytometric measurements of mammalian testicular cells revealed significant differences in acridine orange (AO) stainability between cell types due to changes in nucleic acid content and differentiation of chromatin. Developing sperm cells lose

RNA with a corresponding decrease in red fluoresence and also undergo a reduction of DNA stainability due to both a condensation of sperm chromatin and a reduction of ploidy. Normal spermiogenesis leads to a mature sperm nucleus containing chromatin in which the DNA is highly resistant to in situ thermal denaturation. This resistance can be measured in isolated sperm nuclei heated to 100 C for 5 min prior to staining with AO. The alpha t ratio, ie the ratio of red fluorescence to total fluorescence (red plus green), is often higher for abnormal sperm. Semen samples obtained from patients with testicular carcinomas (usually with unilateral orchiectomy but without further treatment) as well as patients with leukemias and lymphomas (at various stages of chemotherapy treatment) are often characterized by altered patterns of staining with AO prior to and following thermal denaturation. Some of the patterns suggest the presence of a subclass of cells resembling undifferentiated precursor cells normally found in the testis. Thus, both the disease and the treatment have an effect on the development and differentiation of sperm which is detectable by flow cytometry. (no Refs)

20. SUBCLASSIFICATION OF ACUTE LEUKEMIA AND TREATMENT MONITORING BY MULTIPARAMETER FLOW CYTOMETRY (FC) (MEETING ABSTRACT).

Andreef M, Hiddemann W, Melamed MR

Memorial Sloan-Kettering Cancer Center, New York, NY

VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

Human acute leukemia (AL) is commonly diagnosed and classified by morphological and cytochemical criteria, formulated in the French-American-British (FAB) system. Two major subgroups are distinguished: acute lymphoblastic (ALL) and non-lymphoblastic (ANLL) leukemia. We have recently described an objective flow cytometric method to discriminate ALL and ANLL, based on differences in RNA content of G1 cells: ALL has an RNA-Index of 10.2 plus or minus 2.0, ANLL of 20.7 plus or minus 3.8. simultaneously, DNA stemlines and cell cycle distributions are determined (acridine orange two step method (Darzynkiewicz). This assay is routinely carried out at Memorial Hospital. Over 4,000 samples have been studied, among them more than 300 cases of AL which were monitored serially. Flow cytometry and cell separation procedures to fractionate cell populations according to cell size (1 x G velocity sedimentation, elutriation) combined with multiple marker analysis, resulted in a more heterogenous picture of leukemia cell types with regard to their clonal and phenotypic characterization. Two groups are of particular clinical interest: ALL with near-haploid stemlines, and biphenotypic AL. Biphenotypic AL are characterized by the stimultaneous presence of myeloblasts and lymphoblasts. Both subclasses of AL respond poorly, when treated with standard protocols for ALL and ANLL and require different therapeutic approaches. Further refinement of diagnostic criteria can be expected from assaying chromatin structure in situ (acridine orange FC following RNA hydrolysis and partial denaturation of DNA), deoxynucleotidyl transferase (TdT) and leukemia-associated surface antigens using monoclonal antibodies. (1 Ref)

21. ANEUPLOIDY IN ACUTE LEUKEMIA AS DETERMINED BY FLOW CYTOMETRY (MEETING ABSTRACT).

Hiddemann W, Buchner T, Wormann B, Ritter J, Schumann J, Gohde W

Department of Internal Medicine, University of Munster, Munster, W. Germany

VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

Recent progress in technology and methodology has significantly improved the accuracy and validity of flow cytometric analysis thus providing an increased sensitivity for the detection of cell populations with abnormal DNA content. Using a shett flow glass chamber which was hooked up to an ICP 11 with a canberra multichannel analyzer blood and bone marrow aspirates from 133 patients with acute leukemia were analyzed. For the ploidy determination each specimen was mixed with mononuclear cells from normal donors in two different concentrations. DNA index was defined according to Barlogie et al. Improved FCM technology allows rapid, reliable detection of aneuploidies in acute leukemia in a high incidence of cases independent of cellular proliferation thus complementing and may be even challenging chromosome analysis. (no Refs)

22. CORRELATIONS BETWEEN DNA STEMLINE RNA CONTENT AND PARAPROTEIN LEVELS IN MULTIPLE MYELOMA (MEETING ABSTRACT).

Walle A, Andreeff M, Melamed MR, Clarkson BD

Memorial Sloan-Kettering Cancer Center, New York, NY

VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

Twenty-nine patients with multiple myeloma (mM) were investigated at the time of presentation at Memorial Hospital. Fourteen patients were treated, fifteen untreated. DNA and RNA content was measured by acridine orange flow cytometry. Bone marrow plasma cell counts, serum and urine paraprote in levels were also determined. Data was analyzed for possible correlations between DNA stemlines, cellular RNA content of G1 cells, expressed as RNA-Index RI, cell kinetics and immunoglobulin levels in treated and untreated patients. The group of mM with diploid DNA stemline (66%) was distinctly different from the group with hyperdiploid DNA stemline (34%): paraprotein levels were lower (diploid: 278%, hyperdiploid: 570% increased above upper normal limit (IUNL), RNA content was lower (RI: 15.5; hyperdiploid: 27.7), and the number of cells in G1 with high RNA content was also lower (G1H equals 31.1%; hyperdiploid: 71.2%). No difference was found in the number of marrow plasma cells in the diploid (43%) and hyperdiploid (50%) untreated group. Cell cycle analysis did not show a difference in the number of S + G2 + M cells between untreated (10%) and treated patients (10%). RNA content was the same in treated and untreated patients: treated group: diploid RI equals 16.8; hyperdiploid RI equals 27.2; untreated group: diploid RI equals 14.1; hyperdiploid RI equals 28.0. Paraprotein levels, however, were lower in the treated groups (diploid: untreated 305% IUNL, treated 246% IUNL; hyperdiploid: untreated 790% IUNL, treated 423% IUNL. IgA myelomas had higher paraprotein (1148% IUNL) than IgG myelomas (256% IUNL). The prognostic value of the parameters investigated, alone or in combination, will be determined in a prospective study. (1 Ref)

23. QUANTITATIVE CYTOLOGY IN MYELOMA RESEARCH (MEETING ABSTRACT).

Barlogie B, Alexanian R, Latreille J, Smallwood L, Swartzendruber D, Maddox AM

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VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

The previously reported high incidence of DNA flow cytometrically detectable incidence of aneuploidy in patients with multiple myeloma has been further validated in 161 patients, with an overall incidence of 70%, regardless of disease status. A 75% incidence of aneuploidy in patients with active disease exceeded the 15% noted in patients studied in remission. We will report on the frequency distribution patterns of ploidy levels as a function of disease status at time of study (diagnosis, remission, relapse, primary treatment failure), tumor burden, M-protein type and concentration. Overall survival of a subgroup of patients was found to be effected by ploidy level and pre-treatment tumor cell labelling index, regardless of tumor burden at diagnosis. Additional measurements of RNA content, which was found to be markedly higher in plasma cells than in any other hemopoietic cells, proved to be helpful in identifying the occasional patient with a diploid high RNA content tumor cell population. Evaluation of peripheral blood in 30 patients without plasma cell leukemia indicated 4 instances of discrete ploidy abnormality of the same degree as was found in marrow or extramedullary sites. With a median follow-up time in patients with serial observations of approx 1-2 yr, definitive evidence of ploidy changes with the development of drug resistance appears rare. Preliminary data will be presented on the feasibility and additional usefulness of CIg and nucleolar antigen content measurements. (no Refs)

24. CORRELATED ANALYSIS OF CELLULAR DNA, SURFACE ANTIGENS, AND LIGHT SCATTER IN HUMAN B-CELL LYMPHOMAS (MEETING ABSTRACT).

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Department of Pathology, University of Florida College of Medicine, Gainesville, FL, 32610

VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

Cells from human B-cell lymphomas were studied by correlated flow analysis of cellular DNA, surface antigens, and forward angle light scatter. These tumors contain surface immunoglobulin (SIg)-bearing neoplastic B lymphocytes as well as varying numbers of non-neoplastic cells (mainly T-cells). Propidium iodide was used to stain DNA and fluorescein isothiocyanate (FITC)-conjugated antibodies were used to label SIg and T-cell antigens. A Becton-Dickinson fluorescence activated cell sorter (FACS-II) linked to a Hewlett-Packard 9845T microcomputer was used to provide 3-parameter correlated data acquisition with 256 measurement levels for each parameter. Using multiparameter analysis, differences in cellular DNA between predominantly neoplastic cells and non-neoplastic cells from the same tissue were shown. Single parameter DNA analysis revealed no obvious abnormalities in some of these cases. This approach also allowed detection of both diploid and tetraploid neoplastic cells within the same tumor. Although in some instances, light scatter distributions permitted separation of aneuploid from diploid cell populations, in general, light scatter was not a good discriminator between neoplastic and non-neoplastic cells. (no Refs)

25. DNA CONTENT AND KINETIC CHARACTERISTICS OF NON-HODGKIN'S LYMPHOMA: DETERMINED BY FLOW CYTOMETRY AND AUTORADIOGRAPHY.

Costa A, Mazzini G, Del Bino G, Silvestrini R

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Cytometry; 2(3):185-188 1981

Samples of malignant lymph nodes obtained from 74 non-Hodgkin's lymphoma (NHL) patients were cultured; DNA content and 3H-thymidine labeling index (LI) were determined. Propidium iodide was the DNA-specific fluorescence dye used in cytofluorography. Ploidy was expressed as the ratio of relative DNA content of human lymphoid G0/1 cells to that of chicken red blood cells. Of the NHL, 45/74 (61%) were aneuploid, and 91% of those showed a hyperdiploid DNA content. The max frequency of aneuploid tumors (72%) in comparison to diploid tumors (28%) was found in the group with unfavorable histology (original Rappaport classification), but the observation was not significant. Tumors with high proliferative activity showed a significantly (p less than 0.01) lower percentage of cells in G0/1 and a higher percentage of cells in S (P less than 0.01) than those with low proliferative activity. An analysis of 21 cases with a homogenous cell population indicated that the S phase fractions, as determined by cytofluorometry and autoradiographic LI, are correlated (r = 0.95, p less than 0.01). (19 Refs)

26. SPONTANEOUS TRANSFORMATION: DEVELOPMENT OF A MODEL SYSTEM - PRELIMINARY FLOW KARYOTYPE ANALYSIS (MEETING ABSTRACT).

Cram LS, Wilder M, Bartholdi M, Travis G, Jett J, Kraemer PM

Experimental Pathology Group and Life Sciences Division, Los Alamos National Laboratory, Los Alamos, NM, 87545

VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

A Chinese hamster cell system was developed to provide a model system in which the spontaneous and gradual acquisition of tumorigenic properties could be quantitated. Individual Chinese hamster fetuses were used to start primary cultures which were then passaged on both solid and fenestrated matrices through crisis phase. Following crisis, cells emerged that displayed a shortened doubling time, were aneuploid, and were capable of producing tumors in athymic mice following additional passages in culture. Flow instrumentation developed specifically for obtaining high resolution flow karyotypes will be described, along with flow karyotypes of cells taken at several stages of malignant progression. (no Refs)

27. COMPARISON OF ACRIDINE ORANGE AND ETHIDIUM BROMIDE/MITHRAMYCIN STAINING FOR FLUORESCENCE ANALYSIS OF DNA (MEETING ABSTRACT).

Eisert RM, Andreeff M, Eisert WG, Melamed M

Memorial Sloan-Kettering Cancer Center, New York, NY

VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

Density separated mononuclear bone marrow cells have been taken from patients with malignant hematological disorders (mostly acute leukemia). Samples showing different ploidy levels after acridine orange staining and three parameter DNA-RNA nuclear diameter analysis using a laser excited flow system (Ortho FC 200) were reexamined after ethanol fixation and ethidium bromide/mithramycin staining using a mercury arc excited flow system (ICP 22). The coefficient of variation for the G1 peak in the latter system was found smaller after appropriate adjustments. The higher resolution together with better statistics did show small variations in the ploidy level more clearly, however, the same ploidy levels were found. These data indicate, that acridine orange staining after Triton-X treatment as well as ethidium bromide/mithramycin staining after ethanol fixation result in equivalent and stoichiometrical fluorescence of intracellular DNA, and are equally useful in determination of diploid and aneuploid DNA stemlines in the hematopoietic system. (no Refs)

CHROMOSOMAL FRAGILITY AND GENETIC FACTORS PREDISPOSING TO HUMAN CANCER

28. PRENATAL DIAGNOSIS OF FANCONI ANEMIA.

Voss R, Kohn G, Shahem M, Benzur Z, Arnon J, Ornoy a, Yaffe H, Golbus M, Auerbach AD
Dept. Human Genetics, Hadassah-Hebrew Univ. Medical Center, Jerusalem, Israel
Clin Genet; 20(3):185-190 1981

Prenatal diagnosis was performed on a fetus at risk for Fanconi anemia. A high spontaneous (0.30 breaks/cell) and diepoxybutane-induced (0.69 breaks/cell) chromosome breakage rate indicated an affected fetus and the pregnancy was terminated. The anatomic findings in the aborted fetus together with cytogenetic findings in cultured fetal skin fibroblasts confirmed the prenatal diagnosis. (Author abstract) (16 Refs)

29. DNA-REPAIR SYNTHESIS IN ATAXIA TELANGIECTASIA LYMPHOBLASTOID CELLS.

Ford MD, Houldsworth J, Lavin MF
Dept. Biochemistry, Univ. Queensland, Brisbane, 4067, Australia
Mutat Res; 84(2):419-427 1981

DNA-repair synthesis was assayed in lymphoblastoid cells from ataxia telangiectasia (AT) patients and from control cells following exposure to gamma-radiation (10-40 kilorad). NaI isopycnic gradient analysis and 3H-thymidine incorporation into acid-precipitable DNA in the presence of hydroxyurea indicated that AT heterozygote, AT homozygote, and control cells had similar capacities for repair of radiation damage. Rate and extent of dose-dependent inhibition of DNA replication by gamma-radiation were similar in the three groups of cells. Lack of difference between control and AT cells in degree of DNA-synthesis inhibition at the radiation doses used is likely due to a pronounced effect on overall DNA synthesis. (34 Refs)

30. CYTOGENETIC ANALYSIS OF 21 CASES OF ATACTIC TELANGIECTASIA.

Aurias A
Institut de Progenese, 15 rue de l'Ecole de Medecine, 75006 Paris, France
J Genet Hum; 29(3):235-247 1981

Cytogenetic analysis of 2,437 phytohemagglutinin-stimulated lymphocytes from 21 patients with atactic telangiectasia (AAT) revealed 233 (9.5%) with rearrangements of chromosomes 7 and 14, comprising inversions and translocations. A similar abnormality was found in heterozygotes for the gene for AAT, but with a reduced frequency. (20 Refs) (In FRE)

31. REPAIR OF BLEOMYCIN-DAMAGED DNA BY HUMAN FIBROBLASTS.

Hurt MM, Beaudet AL, Moses RE
Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030
J Supramol Struct Cell Biochem; 16(4):303-309 1981

Repair of DNA damage caused by bleomycin (BLM) was studied in fibroblasts from individuals and from patients with diseases due to apparent DNA repair defects. Cells were labeled with (3H)thymidine (TdR). Labeled cells were exposed to 5-500 ug/ml BLM, usually for 30 min, and then subjected to 5-20% alkaline sucrose gradient centrifugation. The fall in DNA mol wt which occurred after exposure to BLM reformed rapidly after removal of the drug. BLM exposure resulted in a fall in DNA mol wt in fibroblasts from patients with ataxia telangiectasia, Bloom syndrome, Cockayne syndrome, and Fanconi anemia. Prelabeled cells from some xeroderma pigmentosum (XP) complementation groups had a higher percentage of low mol wt DNA than did normal cells. The low mol wt DNA in XP cells disappeared upon exposure to BLM. The altered response of XP cells to BLM may be directly related to the abnormal condition of DNA in the cells. (16 Refs)

32. DOUBLE-STRAND BREAKS IN DNA CAUSED BY REPAIR OF DAMAGE DUE TO ULTRAVIOLET LIGHT.

Bradley MO
Merck Inst. for Therapeutic Res., West Point, PA, 19486
J Supramol Struct Cell Biochem; 16(4):337-343 1981

Induction of double strand breaks (DSB) during repair of UV light (UVL) damage was studied in human cells. UV light at doses up to 300 joule (J)/square cm (cm2) did not directly induce detectable DNA DSB in normal (IMR-90) cells irradiated and held on ice until lysis. When IMR-90 cells were irradiated with 100-300 J/cm2 of UVL at room temperature and allowed to incubate in fresh medium at 37 C, a time and dose-related increase occurred in the rate of pH 9.6 elution and therefore number of DNA DSB. DSB began to appear 3 hr after UVL and continued to increase for 51 hr. Since the cells remain attached to the dishes up to 51 hr, and all the cells exclude trypan blue after 24 or 48 hr, the data suggest the DSB are not a secondary result of cell death. Using a neutral filter elution method for measuring small numbers of DSB, UVL was shown not to induce DSB in xeroderma pigmentosum (XP) complementation group A cells; the cells are unable to incise pyrimidine dimer and so cannot initiate excision repair; at the same time they are more sensitive to killing by UVL than normal cells. Thus, excision repair is implicated as a mechanism for DNA DSB formation after UVL. Repair-induced DSB may be potent lesions that lead to cytotoxicity, chromosomal aberrations, deletion mutations, and cellular transformation. (19 Refs)

33. FUNCTIONAL DEFICIENCY OF FIBROBLASTS HETEROZYGOUS FOR BLOOM SYNDROME AS SPECIFIC MANIFESTATION OF THE PRIMARY DEFECT.

Bartram CR, Rudiger HW, Schmidt-Preuss U, Passarge E
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Am J Hum Genet; 33(6):928-934 1981

The effect on the rate of sister chromatid exchanges (SCEs) in Bloom syndrome fibroblasts by cocultivation with Fanconi anemia and xeroderma pigmentosum fibroblasts and with Bloom syndrome heterozygotes was studied. Cells of Fanconi anemia and xeroderma origin reduced the rate of SCEs in Bloom cells by about 45%-50%, just as control cells do. In contrast, heterozygous Bloom cells reduced the rate of SCEs by only 16%-28%. In absolute figures, Fanconi cells reduced the mean rate of SCE in Bloom cells from 55.7 +-5.50 to 27.7 +-6.44, xeroderma cells to 30.5 +-5.73, and control cells to 28.3 +-5.35. Three different cell strains from Bloom syndrome heterozygotes reduced the rate to 40.1 +-8.81, 47.0 +-6.94, and 47.5 +-8.32. There was no effect on any of these cell strains by Bloom syndrome fibroblasts. We interpret the functional deficiency of heterozygous Bloom syndrome fibroblasts as a gene dose effect. It probably represents a specific manifestation of the yet unknown primary defect, because it suggests the existence of a 'corrective factor' that is inactive or absent in homozygous Bloom cells and reduced in heterozygotes. It may be identical with or closely related to the normal gene product at the Bloom locus. (Author abstract) (28 Refs)

34. RETINOBLASTOMA-DEL(13Q14): REPORT OF TWO PATIENTS, ONE WITH A TRISOMIC SIB DUE TO MATERNAL INSERTION. GENE-DOSAGE EFFECT FOR ESTERASE D.

Rivera H, Turleau C, De Grouchy J, Junien C, Depoisse S, Zucker JM
(c/o de Grouchy) U.173 INSERM and E.R.149 CNRS, Hopital Necker-Enfants-Malades, 149, rue de Sevres, F-75743 Paris Cedex 15, France
Hum Genet; 59(3):211-214 1981

Two new cases of del(13)-retinoblastoma occurring in an infant boy and an infant girl are reported. The karyotype of the boy was 46,XY,del(13) (q1307q14.3); he was monosomic for q14.1,q14.2 and probably for a small adjacent segment of q13. The mother carried an insertion in chromosome 20: 46,XX,ins(20;13)(p12;q1307p14.3). A sister had inherited the abnormal maternal chromosome 20: 46,XX,der(20),ins(20;13)mat; she was trisomic for the segment that was monosomic in her brother. The father's karyotype was normal. The karyotype of the female patient was 46,XX,del(13)(q1303q14.3); she was monosomic for q14.1,q14.2 and for practically all of q13. The parents' karyotypes were normal. A remarkable gene-dosage effect was found in esterase D activity, especially when band 13q14 was in triplicate. (11 Refs)

35. HOST CELL REACTIVATION OF UV- AND X-RAY-DAMAGED HERPES SIMPLEX VIRUS BY EPSTEIN-BARR VIRUS (EBV)-TRANSFORMED LYMPHOBLASTOID CELL LINES.

Henderson EE, Long WK
Dept. Microbiology and Immunology, Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Virology; 115(2):237-248 1981

The efficacy of using an infected centers assay, employing herpes simplex virus- infected, Epstein-Barr virus-transformed lymphoblastoid cell lines (LCLs) as components, to study host cell reactivation has been explored. Herpes simplex virus Type 1 (HSV-1) was shown through the infected centers assay to have detectable but varying ability to lytically infect LCLs established from chromosomal breakage syndromes or closely related genetic disorders. The rate of HSV inactivation by UV irradiation was faster in LCLs established from Cockayne's syndrome than in normal LCLs, and faster still in LCLs established from xeroderma pigmentosum. These results indicate that Cockayne's syndrome, while having what appears to be quantitatively normal levels of UV-induced DNA repair replication, shows decreased ability to host cell reactivate UV-damaged HSV. In direct contrast, x-irradiated HSV showed identical survival when assayed on normal LCLs or LCLs established from ataxia telangiectasia showing increased sensitivity to x-irradiation as measured by colony formation. Through the infected centers assay, it has also been possible to demonstrate low levels of multiplicity reactivation of mutagen-damaged HSV in permanently proliferating LCLs. (Author abstract) (43 Refs)

CHROMOSOMES OF HUMAN CELL LINES AND TUMORS IN VITRO

36. CHROMOSOME BANDING ANALYSIS OF HUMAN TUMOR CELLS CLONED IN AGAR (MEETING ABSTRACT).

Trent JM
University of Arizona, Cancer Center, Tucson, AZ, 85724
Third NCI-EORTC Symposium on New Drugs in Cancer Therapy, October 15-17, 1981, Brussells, Belgium European Organization for Research on Treatment of Cancer; :A16 1981

We have utilized the human tumor stem cell assay (HTSCA) to isolate, and cytogenetically study the progenitor/stem cell fraction of a variety of human cancers. Utilization of this system has proved to provide both numeric enhancement of tumor mitoses, and to yield metaphases amenable to detailed chromosome-banding analysis. We recently instituted a detailed study of ovarian neoplasms grown in the HTSCA. Banding analysis revealed a consistent clonal chromosome alteration in the majority of these cancers (del 6q). Additionally, abnormalities of Chromosome 1, and the observation of double minutes (dms) and putative homogeneous staining regions have been observed. Cytogenetic characterization of a variety of additional tumor types including breast, bladder, neuroblastoma, and melanoma have now been successfully performed using this assay system. It appears utilization of this system may represent a potentially important new methodology in the cytogenetic analysis of solid tumors. Finally, detailed karyology of tumor colony forming cells (TCFUs) exposed but resistant to in vitro incubation with various chemotherapeutic agents has been performed. These studies suggest that this system may provide a methodology allowing recognition of cytogenetic changes associated with clonal selection following cytostatic therapy. (1 Ref)

GENE MAPPING STUDIES

37. INVESTIGATIONS ON RADIOSENSITIVE AND RADIORESISTANT POPULATIONS OF DROSOPHILA MELANOGASTER. X. THE RESISTANCE FACTOR RAR-3: GENETICS.

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Mutat Res; 84(2):291-304 1981

Evidence is presented that a single, recessive genetic factor, rar-3, is responsible for increased radioresistance of immature oocytes of the irradiated ROI4 subpopulation of Drosophila melanogaster relative to that of the parent population ROI.

rar-3 is independent of rar-1 and rar-2 (the factors controlling radioresistance in RO1) and is located on chromosome 3 at a map position of about 49.8. (13 Refs)

38. A NEW VARIANT GLYOXALASE I ALLELE THAT IS READILY DETECTABLE IN STIMULATED LYMPHOCYTES AND LYMPHOBLASTOID CELL LINES BUT NOT IN CIRCULATING LYMPHOCYTES OR ERYTHROCYTES.

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Am J Hum Genet; 33(6):935-945 1981

We describe an allele of the human glyoxalase GLO locus that encodes an enzymatically inactive form of the protein. The allele is GLO*3 and its protein product, GLO 3. Circulating blood cells of GLO*2/GLO*3 heterozygotes have just one electrophoretic band that migrates as the normal 2-2 dimer. Lymphoblastoid cell lines and phytohemagglutinin-stimulated lymphocytes from the same individuals have two electrophoretic bands, one with the mobility of the 2-2 dimer and one with the mobility of the 2-1 dimer that is present in GLO*2/GLO*1 heterozygotes. The GLO*3 allele encodes a monomer that has the electrophoretic mobility of GLO 1 but is enzymatically inactive unless it is combined with normal monomers in 2-3 and 1-3 heterodimers. The failure to detect the GLO 3 protein in red cells and unstimulated lymphocytes is attributed to a relatively great instability or small rate of production in those cells. Consistent with this interpretation is the reduction of GLO activity in red cells of GLO*2/GLO*3 and GLO*1/GLO*3 heterozygotes to 65% or less of that in normal homozygotes and heterozygotes, while the activity of GLO*3 heterozygous lymphoblastoid cells is about 80% of normal. In contrast, the GLO activity of lymphoblastoid cells that had one copy of the GLO locus deleted by gamma-irradiation was 50%-60% of normal. Our observations indicate that certain kinds of mutant alleles of the GLO locus, and perhaps other loci, may not be detected in electrophoretic surveys on circulating blood cells only. The segregation of alleles that are not expressed in circulating red and white blood cells could confuse attempts to determine parentage, as they might have in the family described here. The observations also demonstrate the feasibility of mapping human genes by usin g ionizing radiation to create partial chromosome deletions in cultured cells. (20 Refs)

MOLECULAR CYTOGENETICS

39. POLY ADP-RIBOSYLATION AS A PROSPECTIVE MODULATOR OF CHROMATIN STRUCTURE IN THE HELA CELL NUCLEUS.

Jump DB
Georgetown University Medical Center, Washington, DC
Diss Abstr Int [B]; 42(5):1858-B 1981

Several critical issues dealing with understanding the function of poly (ADP-Rib) polymerase in the HeLa nucleus have been addressed: (a) purification and characterization of poly (ADP-Rib) polymerase from HeLa nuclei; (b) determining that histone modification is most prominent during periods of DNA synthesis; (c) distribution of the enzyme and its acceptor proteins in chromatin with particular emphasis on the elucidation of the association of these proteins with extended regions of chromatin undergoing DNA synthesis; and (d) preliminary evidence indicating that poly ADP-ribosylation may function to promote condensation of modified domains resulting in decrease accessibility of chromatin DNA to nucleases. (no Refs)

40. EFFECT OF N-BUTYRATE ON CELL CYCLE PROGRESSION AND IN SITU CHROMATIN STRUCTURE OF L1210 CELLS.

Darzynkiewicz Z, Traganos F, Xue SB, Melamed MR
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Exp Cell Res; 136(2):279-293 1981

In the presence of 1-5 mM n-butyrate, murine leukemic L1210 cells cease proliferation and become arrested in the G1A compartment of the G1 phase. Cells in this compartment are characterized by low RNA content and more condensed chromatin. During unperturbed growth the cell residence times in G1A are of indeterminate duration. The effect of n-butyrate in arresting cells in G1A was concentration-dependent. However, the sensitivity of L1210 cells to this drug was markedly enhanced when cells were treated for longer than one generation (12 hr). Cells arrested in G1A remained viable and when n-butyrate was removed, after a lag period, they resumed progression through the cycle. The effect of n-butyrate on cell progression through various parts of the cycle was studied in a stathmokinetic experiment. DNA in situ in nuclei of n-butyrate-treated cells had lowered (by 2-8 C) stability to thermal denaturation and increased (by 15%) accessibility to DNase I. DNA in situ in the nuclei of n-butyrate-treated cells also showed decreased sensitivity to acid-induced denaturation. Changes in chromatin were seen in all cells, regardless of cell cycle phase, within the first hr after addition of n-butyrate. Mitotic cells, however, reacted to n-butyrate more rapidly than interphase cells. The observed changes in L1210 cells are most likely a consequence of histone modifications (acetylation of inner histones, dephosphorylation of histone H1) induced by n-butyrate. (41 Refs)

41. INTEGRATION OF FOREIGN GENOME FRAGMENTS INTO CELLS TRANSFORMED OR COTRANSFORMED WITH FRAGMENTED ADENOVIRAL DNA.

Tikchonenko TI, Chaplygina NM, Kalinina TI, Gartel AL, Ponomareva TI, Naroditsky BS, Dreizin RS
D. I. Ivanovsky Inst. Virology, Acad. Medical Sciences USSR, Moscow 123098, USSR
Gene; 15(4):349-359 1981

DNA integration of highly oncogenic simian adenovirus type 7 (SA7) and non-oncogenic human adenovirus type 6 (Ad6) into the genome of newborn rat kidney cells transformed by fragmented DNA preparations was studied. SA7 and Ad6 transformation, expression of integrated viral sequences, Ad6-pBR322 plasmid cointegration comprised the study. Intact DNA transformation, transformation by fragmented DNA, shortening of integrated DNA, and competence of eukaryotic cells are discussed. Reassociation kinetics and spot hybridization were employed. DNA was fragmented with the specific endonucleases SalI and endonuclease BglII. Cells transformation by fragmented DNA resulted in integration of the left-hand fragment and other regions of the viral genome with the oncogene. Integrated fragments were stable during numerous passages of cell lines. In the case of the Ad6-transformed cell line integrated fragments were not expressed. Mass losses of 25-50% occurred with the integration of SA7 DNA fragments. The linear form of pBR322 plasmid contributed to the Ad6 DNA integration into the genome of the transformed cell. (40 Refs)

42. EXTRACHROMOSOMAL BOVINE PAPILLOMAVIRUS TYPE 1 DNA IN HAMSTER FIBROMAS AND FIBROSARCOMAS.

Pfister H, Fink B, Thomas C
Institut fur Virologie, Zentrum fur Hygiene, Hermann-Herder-Strasse 11, 78 Freiburg, W. Germany

Virology; 115(2):414-418 1981

BPV 1-induced hamster tumors were used as model system to investigate the state of viral DNA in non-virus-producing tumors arising from papillomavirus infection. DNAs from a fibroma and three fibrosarcoma were analyzed for BPV 1 DNA by the Southern blot technique. The vast majority of viral DNA persists in a nonintegrated form, since; (i) supercoiled BPV-DNA can be purified bv CsCl-ethidium bromide equilibrium centrifugation, (ii) restriction endonucleases, which do not cut viral DNA, do not change the DNA pattern in comparison to uncleaved samples, and (iii) digests of BPV-DNA with restriction enzymes HpaI, HpaII, and HhaI, respectively, lead to identical patterns with DNA from hamster tumors and from warts. Less than one genome equivalent per cell could persist in an integrated form. Virus-specific, high-molecular-weight DNA in the tumors may be interpreted as oligomeric or catenated DNA. Cleavage analysis of tumor DNA with the restriction enzymes HpaII and HhaI, both sensitive to DNA methylation, provided no evidence for methylation of BPV 1 DNA in hamster tumors. (Author abstract) (28 Refs)

43. GENETIC MAPPING OF ENDOGENOUS MOUSE MAMMARY TUMOR VIRUSES: LOCUS CHARACTERIZATION, SEGREGATION, AND CHROMOSOMAL DISTRIBUTION.

Traina VL, Taylor BA, Cohen JC
Dept. Microbiology and Immunology, Tulane Medical Center, New Orleans, LA, 70112

J Virol; 40(3):735-744 1981

The restriction endonuclease EcoRI has been used to study the inheritance of strain differences in endogenous mouse mammary tumor virus DNA sequences. This enzyme, which cleaves at only one site within the nondefective viral genome, generates DNA fragments containing mouse mammary tumor virus sequences which vary in size according to the locations of EcoRI restriction sites in the flanking mouse sequences, thereby defining unique integration sites of the viral genome. Recombinant inbred strains of mice have been used to study the inheritance of these DNA fragments which hybridize to mouse mammary tumor virus cDNA sequences. The results define 11 segregating units consisting of one or two fragments. These units were shown to segregate among the recombinant inbred strains, and in some instances linkage was established. Two units were shown to be linked on chromosome 1. Another unit was mapped to chromosome 7, which is presumably identical to the previously defined genetic locus Mtv-1. One other mouse mammary tumor virus locus was tentatively assigned to chromosome 6. The results are consistent with the view that integration of mouse mammary tumor virus can take place at numerous sites within the genome, and once inserted, these proviruses appear to be relatively stable genetic entities. (Author abstract) (45 Refs)

EFFECTS OF EXOGENOUS AGENTS ON CHROMOSOMES

44. EFFECT OF LOW DOSE RATE IONIZING RADIATION ON THE DIVISION POTENTIAL OF CELLS IN VITRO. VIII. CYTOGENETIC ANALYSIS OF HUMAN FIBROBLASTS.

Bourgeois CA, Raynaud N, Diatloff-Zito C, Macieira-Coehlo A
Laboratoire de Pathologie Cellulaire, Institut des Cordeliers, 75005 Paris, France

Mech Ageing Dev; 17(3):225-235 1981

Human embryonic and adult cells were irradiated with fractionated doses of low dose rate ionizing radiation starting early during their lifespan. Adult cells were found to be more sensitive than fetal cells to ionizing radiation in terms of the number of cells produced during the lifespan of the control and the irradiated cultures. Phase III adult control cells had fewer chromosomal aberrations than Phase-III embryonic control cells. After irradiation there was an increase in chromosomal aberrations in adult cells but no increase in embryonic cells beyond those found in the control cultures. It is suggested that cells that have a higher potential for chromosomal rearrangements survive better after low dose rate ionizing radiation. (Author abstract) (19 Refs)

45. NON RANDOM POSITION OF METAPHASIC CHROMOSOMES: A STUDY OF RADIATION INDUCED AND CONSTITUTIONAL CHROMOSOME REARRANGEMENTS.

Dutrillaux B, Viegas-Pequignot E, Aurias A, Mouthuy M, Prieur M
Institut de Progenese, 15, rue de l'Ecole de Medecine, F-75270 Paris Cedex 06, France

Hum Genet; 59(3):208-210 1981

The position of rearranged chromosomes in cases of reciprocal translocation and dicentric-acentric formation was studied. The chromosomes were obtained after induction by irradiation at the G0 phase. Rearranged chromosomes had a clear tendency to be closer together than their normal homologues; the tendency disappeared in longer cultures and when many different constitutional reciprocal translocations were considered together. The chromosomes remained adjacent at the following metaphase; metaphase plates reflected the new arrangement. (7 Refs)

46. THE INFLUENCE OF ANOXIA OR OXYGENATION ON THE INDUCTION OF CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES BY 15-MEV NEUTRONS.

Prosser JS, Stimpson LD
Natl. Radiological Protection Board, Chilton, Didcot, Oxon OX11 ORQ, England

Mutat Res; 84(2):365-373 1981

Human lymphocytes were analyzed for dicentric and total aberrations after 15 million electron volt megavoltage neutron irradiation given during anoxia or oxygenation. The oxygen-enhancement ratio ranged from 3.7 to 1.6. Oxygen evidently does not act as a dose-modifying agent in the system. Values for relative biologic effectiveness (RBE) were greatest at low neutron doses where the presence of oxygen did not affect the value obtained. At high doses, RBE values were greater for aberrations induced during anoxia. (30 Refs)

47. INVESTIGATIONS ON RADIOSENSITIVE AND RADIORESISTANT POPULATIONS OF DROSOPHILA MELANOGASTER. XI. THE RESISTANCE FACTOR RAR-3: EFFECTS IN IMMATURE OOCYTES.

Nothel H
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Mutat Res; 84(2):305-313 1981

X-ray-induced dominant lethals, homologous interchanges, X-chromosome losses, and sex-linked recessive lethals in immature oocytes (approx stage 7) of radioresistant Drosophila melanogaster strain ROI4 were studied. Dose-reduction factors previously estimated for rar-3, the genetic factor proposed to be responsible for radioresistance, were validated. Thus, rar-3 is a single genetic factor that differentially affects x-ray-induced genetic damage in ROI4 oocytes. No differences in the type of recessive lethals induced by rar-3 or rar-3+ or in recombination frequencies of the two genotypes were demonstrated. (8 Refs)

48. SPONTANEOUS AND INDUCED CHROMOSOME ABERRATIONS IN BONE MARROW OF MICE OF DIFFERENT STRAINS AND AGE.

Lil'p IG, Korogodina IuV
Lab. Experimental Genetics, Inst. Medical Genetics, Moscow, USSR
Tsitologiia; 23(10):1174-1179 1981

The frequency of spontaneous and radiation- or thiophosphamide induced chromosome aberrations was studied in the bone marrow of 2-and 10-17 mo old A/He, 101/H, CBA, C57BL/6, and BALB/c mice . The level of induced chromosome aberrations in C57BL/6 mice did not depend upon the age, while the mice of other strains showed age-dependent increase of the frequency of chromosome aberrations. (40 Refs) (In RUS)

49. INDUCTION OF CHROMOSOME ABERRATIONS IN MAMMALIAN CELLS BY TEMPERATURE-SENSITIVE SV40 MUTANT.

Gorbunova LV, Varshaver NB, Lelikova GP, Shapiro NI
Inst. Molecular Genetics, Moscow, USSR
Biol Nauki; (10):75-78 1981

To evaluate the mutagenic effect of simian virus SV40, cultured Syrian hamster cells were infected with temperature-sensitive (ts) SV40 mutant at 33 C and 40 C. Significant increase of the frequency of chromosome aberrations was recorded only at permissive temperature (33 C), while at restrictive temperature (40 C), SV40-ts failed to induce chromosome aberrations. (13 Refs) (In RUS)

50. INDUCTION OF SISTER CHROMATID EXCHANGES AND BACTERIAL REVERTANTS BY ORGANIC EXTRACTS OF AIRBORNE PARTICLES.

Lockard JM, Viau CJ, Lee-Stephens C, Caldwell JC, Wojciechowski JP, Enoch HG, Sabharwal PS
Graduate Center for Toxicology, Univ. Kentucky, 212 Medical Annex 5, Lexington, KY, 40506
Environ Mutagen; 3(6):671-681 1981

The genotoxicity of organic extracts of airborne particles collected in Lexington, Kentucky was evaluated. In sister chromatid exchange (SCE) assays conducted in human lymphocytes, extracts of all samples induced dose-related increases in number of SCEs. Concentrations of 60 or 80 ug extract/ml caused approximate doubling of background frequency of SCE, to 7.0-9.6 SCE/cell. No metabolic activation was used, indicating that compounds contained in the samples were either direct acting or activated by the lymphocytes. Addition of S9 activation induced negligible increases in number of SCEs for all samples in V79 Chinese hamster fibroblasts. Concentrations of more than 60-80 ug of the extracts were toxic to both human lymphocytes and V79 cells, inhibiting cell division and causing cell lysis. Dose related increases in number of bacterial revertants were induced by all of the organic extracts tested in the Ames assay with both TA98 and TA100. Addition of S9 caused no significant differences in reversion frequencies. (41 Refs)

51. THE INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY K-REGION EPOXIDES AND SOME DIHYDRODIOLS DERIVED FROM BENZ[A]ANTHRACENE, DIBENZ[A,C]ANTHRACENE AND DIBENZ[A,H]ANTHRACENE.

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Mutat Res; 84(2):389-398 1981

Benz[a]anthracene (BA), dibenz[a,c]anthracene (DB[a,c]A), dibenz[a,h]anthracene (DB[a,h]A), and some of their metabolites were studied for induction of sister chromatid exchanges (SCE) in cultured Chinese hamster ovary cells. BA and 1,2; 5,6-; 8,9-; and 10,11-diols induced some SCE, but they were not as active as either benz[a]anthracene 5,6-oxide, which induced an approx 2-fold increase in SCE at 1 ug/ml, or trans-3,4-dihydro-3,4-dihydroyxbenz[a]anthracene. Despite the strong cytotoxicity of DB[a,c]A, it did not induce SCE. However, all DB[a,c]A metabolites tested (1,2-; 3,4-; and 10,11-dihydrodiols) induced SCE in a dose-dependent manner; trans-1,2-dihydro-1,2-dihydroxybenz[a,c]anthracene (4 ug/ml) induced a greater than 4-fold increase in SCE. DB[a,h]A was only weakly active. Trans-3,4-dihydro-3,4-dihydroxydibenz[a,h]anthracene was the most active DB[a,h]A metabolite, producing a greater than 3-fold increase in SCE at 2 ug/ml. Dibenz[a,h]anthracene 5,6-oxide actively induced SCE in a dose-dependent manner, whereas the 5,6-and 1,2-diols were almost inactive. K-region 5,6-epoxides derived from BA and DB[a,h]A were more active than the parent hydrocarbon in inducing SCE. Data suggest that when activated, the three polycyclic aromatic hydrocarbons studied can be metabolized to the ultimate carcinogen in CHO cells possessing some microsomal monooxygenase. (35 Refs)

52. SPONTANEOUS AND BUSULPHAN-INDUCED SISTER-CHROMATID EXCHANGE (SCE) FREQUENCIES IN HAEMATOLOGICALLY NORMAL HUMAN BONE MARROW AND LYMPHOCYTES.

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Mutat Res; 84(2):399-407 1981

Sister chromatid exchange (SCE) frequencies were determined in untreated and busulfan (BUS)-exposed lymphocytes and in bone-marrow cells from 17 untreated, hematologically normal patients with primary breast carcinoma or melanoma. Spontaneous SCE frequencies were in the range 3.13-11.07/cell for bone-marrow cells and from 8.13-13.30/cell for lymphocytes. SCE values were consistently lower in bone-marrow cells than in lymphocytes in all but one patient. Inter-patient variability in spontaneous SCE distribution was significant for both bone-marrow cells and lymphocytes. No correlation was noted between bone-marrow and lymphocyte SCE distribution, indicating that SCE values for the two tissues could be a tissue-specific phenomenon. The SCE technique gave a good quantitative assay of BUS-induced chromosome damage: both lymphocytes and bone-marrow cells from 14 of the cancer patients exhibited similar increases in SCE frequencies following in vitro exposure to the same BUS concentrations. Lymphocytes were in stage G0 when the drug was added prior to culturing, whereas bone-marrow cells were dividing: BUS may bind to DNA equally well at different stages of the cell cycle. Similar gradients of regression lines were obtained for pooled SCE data from bone marrow samples exposed to 0-2.0 ug/ml BUS, for bone-marrow samples exposed to up to 5.0 ug/ml BUS, and for previous lymphocyte SCE data; the ability of BUS to induce SCE is apparently the same in both tissues. (22 Refs)

53. SISTER CHROMATID EXCHANGE INDUCTION AND CELL CYCLE INHIBITION BY ANILINE AND ITS METABOLITES IN HUMAN FIBROBLASTS.

Wilmer JL, Kligerman AD, Erexson GL

Dept. Genetic Toxicology, Chemical Industry Inst. Toxicology, P.O. Box 12137, Research Triangle Park, NC, 27709

Environ Mutagen; 3(6):627-638 1981

The effects of aniline HCL, para-aminophenol (pAP), ortho-aminophenol (oAP), acetanilide (AA), para-hydroxy-acetanilide (pOHAA), ortho-hydroxyacetanilide (oOHAA), and N-phenylhydroxylamine (PHA) on sister chromatid exchange (SCE) and cell proliferation were investigated in human fibroblasts. Although considerable diversity in cytological effects was observed, oAP and PHA were the only compounds found to induce dose-dependent increases in SCE. With 0.1 milliM (mM) oAP the SCE frequency was doubled; at 0.1 mM PHA the SCE frequency was increased 40% over controls. PHA appeared to inhibit cell proliferation to a greater extent than oAP. A slowing of the cell cycle was observed with 0.01 mM PHA and with 0.1 mM oAP. Concentrations of 0.5 mM PHA and 0.3 mM oAP caused extensive cell death. Aniline HCL induced minimal but significant increases in SCE. On the basis of SCE frequency per millimole, oAP was approx 3.1x more potent than PHA; PHA was approx 87.4x more potent than aniline HCl. pOHAA (10 mM) induced pronounced inhibition of cell replication but no increases in SCE. Determination of mitotic indices proved to be far less sensitive as an indicator of toxicity than cell cycle analysis. (56 Refs)

54. BASELINE AND SODIUM ARSENITE-INDUCED SISTER CHROMATID EXCHANGES IN CULTURED LYMPHOCYTES FROM PATIENTS WITH BLACKFOOT DISEASE AND HEALTHY PERSONS.

Wen WN, Lieu TL, Chang HJ, Wuu SW, Yau ML, Jan KY

(c/o Jan) Inst. Zoology, Academia Sinica, Taipei 115, Taiwan

Hum Genet; 59(3):201-203 1981

Baseline and arsenic-challenged sister chromatid exchange (SCE) frequencies were examined in short-term cultured lymphocytes from Blackfoot disease patients (BFP) and healthy persons (HP). A significantly higher baseline SCE was found in BFP than in HP. Sodium arsenite was effective in increasing SCE frequency and delaying cell growth of lymphocytes from both BFP and HP. No significant difference between BFP and HP was found either in the SCE increment induced by sodium arsenite or the progression of cell divisions in cultured lymphocytes. (17 Refs)

55. PATULIN, A FURTHER CLASTOGENIC MYCOTOXIN, IS NEGATIVE IN THE SCE ASSAY IN CHINESE HAMSTER V79-E CELLS IN VITRO.

Thust R, Kneist S, Mendel J

Inst. Pathology, Medical Acad. Erfurt, Nordhauser Strasse 74, 50 Erfurt, E. Germany

Mutat Res; 103(1):91-97 1982

Clastogenicity of patulin (PT) was studied in Chinese hamster V79-E cells. Experiments demonstrated PT was a direct-acting clastogenic agent. Clastogenic activity was abolished when S9 mix (9,000 x gravity liver supernatant) was added, even at the S9-free cytotoxic concentration of 10(-5) M. Clastogenic activity was detected only within a narrow range: 22% aberrant mitoses at 5 x 10(-6) M and 8% at 2.5 x 10(-6) M. The concentration 10(-5) M was toxic. In further studies with V79-E cells, clastogenic effect depended on amount of incubation fluid as well as on number of cells treated, ie it depended on the number of molecules available per target cell. Within a dose range permitting survival of cells, PT did not induce an increase in the rate of sister chromatid exchange (SCE). Experiments on aberration kinetics showed a max rate 24 hr after treatment; SCE staining revealed that most cells underwent two S phases during this period. PT clastogenicity may be caused by interaction with chromosomal proteins; DNA does not appear to be the virtual target of this mycotoxin. (25 Refs)

56. CLASTOGENICITY AND SISTER CHROMATID EXCHANGE INDUCTION BY FTORAFUR.

Vrba M, Adamek R, Blasko M, Brezina V, Chrz R, Goetz P, Michalova K, Musilova J, Novotna B, Pogosianz HE, Raposa T, Siracky J, Sokova OI, Thust R, Ujhazy V, Volgareva GM

Pediatric Res. Inst., 662 62 Brno, Czechoslovakia

Neoplasma; 28(4):397-402 1981

The main effect of Ftorafur at the chromosomal level is the induction of chromatid and chromosome breaks, which is more pronounced in neoplastic or transformed cells than in normal cells. Different cell lines used in the study exhibited both in vitro and in vivo varying sensitivity to Ftorafur. Ftorafur does not increase the frequency of SCE. (Author abstract) (15 Refs)

57. THE ACTION OF TRANSITION METALS ON THE GENOTOXICITY OF SIMPLE PHENOLS, PHENOLIC ACIDS AND CINNAMIC ACIDS.

Stich HF, Rosin MP, Wu CH, Powrie WD

Environmental Carcinogenesis Unit, British Columbia Cancer Res. Centre, 601 W. 10th Ave., Vancouver V5Z 1L3, Canada

Cancer Lett; 14(3):251-260 1981

The capacity of several phenolic compounds to induce chromatid breaks and exchanges in Chinese hamster ovary cells, and the modulating effect of the transition metals Cu++ and Mn++ on the clastogenicity of phenolics were examined. All dihydroxylated and trihydroxylated phenolics induced chromatid breaks and exchanges. Addition of S9 mixture or transition metals enhanced clastogenicity of some phenolics but reduced it in others. (35 Refs)

58. INDUCTION BY INORGANIC METAL SALTS OF SISTER CHROMATID EXCHANGES AND CHROMOSOME ABERRATIONS IN HUMAN AND SYRIAN HAMSTER CELL STRAINS.

Larramendy ML, Popescu NC, DiPaolo JA
Lab. Biology, NCI, Bethesda, MD, 20205
Environ Mutagen; 3(6):597-606 1981

The frequency of sister chromatid exchange (SCE) and chromosomal aberrations (CAb) induced by several inorganic salts previously tested for transformation in Syrian hamster cells (HEC) was examined. Nontoxic concentrations of inorganic metal salts (sodium arsenite, beryllium sulfate, and nickel sulfate) that caused transformation in HEC increased SCE and CAb in human lymphocytes and HEC. Induced SCE frequencies were similar in the two cell types; increases were dose-related. Compared to control values of 5-18 and 7-20 SCE/cell in human and HEC cells, respectively, metals induced an SCE range of 10-35/cell. Sodium arsenite was most effective in human purified lymphocyte cultures, elevating SCE frequencies from 11.30 +-0.60 to 19.2 +-0.84 and 20.60 +-1.32 at 0.1 and 0.25 ug/ml, respectively. Sodium arsenate, beryllium sulfate, and nickel sulfate similarly increased SCE frequency but at 100x higher concentrations. Sodium arsenite and sodium arsenate, but not sodium tungstate, increased SCE frequency in whole human blood cultures. All tested inorganic metals except sodium tungstate induced SCE in HEC to approx 8x control values. CAb induction paralleled SCE induction, with chromatid aberrations being most frequent. (48 Refs)

59. ULTRASONIC INDUCTION OF SISTER CHROMATID EXCHANGES IN HUMAN LYMPHOCYTES.

Haupt M, Martin AO, Simpson JL, Iqbal MA, Elias S, Dyer A, Sabbagha RE
(c/o Martin) Dept. Obstetrics and Gynecology, Northwestern Univ. Medical, Chicago, IL
Hum Genet; 59(3):221-226 1981

Sister chromatid exchange (SCE) frequencies were analyzed using 'real-time' ultrasound as an indicator of DNA damage induced in human lymphocytes. Studies showed consistent small effects of ultrasound on SCE frequencies. A range of exposure times and intensities was tested in a series of blind, randomized, in vitro experiments under spatial and sonographic conditions simulating exposure of a gravid abdomen and uterus. Minimizing the numbers and lengths of exposure per patient appears prudent. (30 Refs)

GENERAL REVIEWS

60. CANCER CYTOGENETICS: A RE-EVALUATION OF ITS SIGNIFICANCE.

Hsu TC
Dept. Cell Biology, Univ. Texas, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Med Pediatr Oncol; 9(5):524-525 1981

Cytogenetics of familial and nonfamilial human cancers and of cancers in experimental animals are described. Specific chromosomal aberrations have been associated with human cancers including retinoblastoma, Wilm's tumor, and renal cell carcinoma. Chromosomal changes in medullary thyroid neoplasia and Gardner's syndrome have been reported. Nonrandom chromosomal alterations have been observed in murine T-cell leukemia and in neurogenic tumors induced in rats. Chromosomal aberrations have been noted in various human leukemias and lymphomas. (no Refs)

61. DO LEUKEMIA CELLS ALWAYS HAVE CHROMOSOME DAMAGE?.

Gahrton G
No affiliation given
Lakartidningen; 78(45):4015-4016 1981

Recent studies on chromosome aberrations in leukemia are discussed. It was found possible to stimulate leukemia cells in chronic lymphocytic leukemia (CLL) by so-called polyclonal B-cell mitogens, mainly lipopolysaccharides from Escherichia coli and Epstein-Barr virus, which mitogens reveal chromosome aberrations in most cases. In addition, an extra chromosome 12 was found in approx 50% of all cases of CLL. It was possible to demonstrate some form of clonal chromosome aberration in 24/24 cases of acute nonlymphoblastic leukemia by cell synchronization with methotrexate pretreatment, while chromosome aberrations were demonstrated by the direct method in 16/24 cases only. The findings indicate that the incidence of leukemias with chromosomal aberration is considerably higher than had been hitherto demonstrable by the conventional techniques, and that the leukemic clone may always be aberrant. The detection of chromosome markers on leukemia cells is of great clinical significance, eg, in the diagnosis of smouldering leukemia and preleukemia, in therapy evaluation, and for prognosis. Recent results indicate that certain aberrations, eg, 8;21 aberration in acute leukemia, are associated with relatively good prognosis, while others, eg, extra chromosome 12 in CLL, imply relatively poor prognosis. (9 Refs) (In SWE)

62. NEOPLASIA ASSOCIATED WITH ANOMALOUS SEXUAL DEVELOPMENT AND ABNORMAL SEX CHROMOSOMES.

Scully RE
James Homer Wright Pathology Lab., Massachusetts General Hosp., Boston, MA, 02114
Pediatr Adolesc Endocrinol; 8:203-217 1981

Risk for development of malignant and benign genital neoplasms in children with intersexual state or abnormal sex chromosomes is reviewed. The children with cryptorchidism were shown to be 10-15x as predisposed to the development of malignant germ cells in descended testes. Bilateral testicular tumors were found to develop in small percent of male with adrenogenital syndrome. Testicular feminization is associated with such proliferative disorders as germ cell tumors, hamartomas, and adenomas. Gonadal dysgenesis is associated with gonadoblastomas, which are frequently complicated by seminomas or dysgerminomas. Wilms' tumors were reported in the patients with mixed gonadal dysgenesis. The patients with Klinefelter's syndrome were found to have germ cell tumors located in the mediastinum, retroperitoneum, and pineal regions. (46 Refs)

63. THE ROLE OF CYTOGENETIC TESTS IN DETECTION AND PREVENTION OF CANCER.

Bishun NP
Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey, England
J Surg Oncol; 18(3):287-304 1981

Although simplified and improved techniques have increased at a fast rate in recent yr, a great number of compounds released into our environment still remain untested. It has been estimated that between 80-90% of human cancer is a result of exposure to such compounds, and if by the application of short-term mutagenic tests, the use of many of these compounds can be severely restricted, an enormous impact can be made on the solution of human health problems. Batteries of mutagenic tests have established an empirical relationship between mutagenesis and carcinogenesis, and, in view of the cost in terms of time and money, short-term tests are playing an important role in first detecting, and second, eliminating potential hazards in our environment. The use of bacteria and other unicellular organisms in these assay systems has met with much criticism; due to the fact that the DNA materials affected do not directly relate to that of man. However, in conjunction with other tests, utilizing human and other mammalian cells, firm conclusions can be drawn regarding the potential hazards of certain chemicals. Recent advances in cytogenetic tests (eg, banding chromosomes and sister chromatid exchange) have improved the sensitivity of chromosomal tests and, in so doing, have rendered them more useful in the selecting out process that can reduce substantially the mutagenic and carcinogenic hazards caused by chemicals and other deleterious agents in the environment. (Author abstract) (45 Refs)

64. ETHYLENE OXIDE (ETO): EVIDENCE OF CARCINOGENICITY.

Coene RF
National Inst. for Occupational Safety and Health, Cincinnati, OH
Vet Hum Toxicol; 23(6):439-443 1981

The potential of ethylene oxide (EtO) as an occupational carcinogen is discussed. Production, use, potential for occupational exposure, evidence of carcinogenicity in experimental animals, mutagenic and reproductive effects, epidemiologic evidence of cancer in humans, exposure standards, and guides are reviewed. Results in sub-mammalian test systems (Salmonella typhimurium, Escherichia coli, Neurospora crassa, Tradescantia paludosa, and Drosophila melanogaster) have indicated mutagenic properties of EtO. EtO has caused statistically significant increases in mononuclear cell leukemia in female Fisher 344 rats. Among male Fisher 344 rats, EtO induced peritoneal mesothelioma originating in the testicular mesothelium. Investigation of possible adverse effects (analysis of chromosomal aberrations in lymphocytes for all exposed workers and sperm analysis for the men) has shown higher incidence of aberration and sister chromatid exchange among workers exposed to EtO. Cases of peripheral neuropathy among exposed workers have been reported. The present standard (1-10 ppm as 8 hr time-weighted av) may need to be reexamined; its adoption preceded recognition of the carcinogenic potential of EtO and was intended only to protect against acute and nonmalignant chronic effects. (no Refs)

65. DOSIMETRY OF THE ATOMIC BOMB SURVIVORS.

Sinclair WK, Failla P, Bond VP, Loewe WE, Kerr GD, Auxier J, Wyckoff OH, Maruyama T, Schull JW, Land EC, Dobson LR, Mays WC, Seymour J
Argonne Natl. Lab., 9700 South Cass Ave., Argonne, IL, 60439
Radiat Res; 88(3):437-447 1981

A summary of information presented at the Late Effects Workshop on Dosimetry of the Atomic Bomb Survivors was compiled. The relevance of findings obtained on Japanese atomic bomb survivors for the determination of radiation risk estimates is discussed through a review of the history, status and implications of the dosimetry of the survivors. In a study of the radiobiological significance of the HIroshima/Nagasaki data, it was determined that there are qualitative differences between the two cities which suggest the presence of a high-linear energy transfer component at Hiroshima. These include the shapes of the curves for chromosomal aberrations and a difference in the spectrum of leukemia types in the two cities. In another presentation, it was suggested that for Hiroshima, at 2 kilometers, the T65 neutron doses were 9x too high, and the gamma doses 4x too low; the uncertainties (approx a factor of 2) in these estimates can be reduced by additional effort. Another presentation reviewed problems associated with calculating dosimetry for the Japanese atomic bomb survivors. The Ichiban studies showed that the sulfur-activation data from Hiroshima and Nagasaki were in reasonable agreement with T65 doses. The difficulty in correlating the chromosome aberration results found in the two cities with the doses predicted by new calculations is considered. The role of the National Council on Radiation Protection and Measurements in Hiroshima and Nagasaki dosimetry is discussed. Primary points brought out in discussions associated with the symposium are listed. (7 Refs)

66. GENETIC AND BIOCHEMICAL STUDIES WITH ATAXIA TELANGIECTASIA.

Huang PC, Sheridan RB
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205
Hum Genet; 59(1):1-9 1981

Correlation of the clinical symptomatology with the genetics and biochemical studies of cultured cells derived from patients with ataxia telangiectasia (AT) is presented in a review. The genetics and symptomatology of AT are described. The susceptibility of patients with AT to sino-pulmonary infection and predisposition toward lymphoreticular malignancy may be caused by immunodeficiency involving humoral and/or the cellular immune system. Approx 10% of patients with AT develop cancer. Response of AT patients to radiation is discussed. Recent cytogenetic, cellular, and biochemical studies are reviewed which support the hypothesis that a defect in DNA repair is responsible for the many manifestations of AT. A table summarizes biochemical studies of 25 factors in 19 cell lines, all but four of which were derived from AT homozygotes. The biochemical evidence indicates that the defect specifically reduces the cell ular capacity to remove bases and nucleotides damaged by ionizing radiation, without affecting the cells' ability to scavenge free radicals or to rejoin breaks in the sugar-phosphate backbone of DNA. (72 Refs)

67. THE DISSECTION AND RECONSTRUCTION OF GENES AND CHROMOSOMES (NOBEL ADDRESS).

Berg P
Dept. Biochemistry, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Angew Chem; 93(10):885-893 1981

The development of understanding of the structure and function of genes and chromosomes is reviewed. Early research established that genes controlled the production of proteins. Analysis of DNA from viruses and bacteria disclosed the double-helix structure and purine-pyrimidine base-pair composition of DNA. Studies with polyoma and SV40 viruses allowed mapping of genes producing specific proteins. SV40 was shown to have different life cycles in primate and non-primate cells. Transformation of host cells by SV40 viruses was demonstrated, indicating that viruses could produce heritable changes in host-cell genetic material. Recombination experiments combined viral DNA from SV40 and bacterial DNA from Escherichia coli. Viral and bacterial DNA have since been incorporated into the genome of mammalian cells. Mammalian cells with bacterial genes have been shown to produce bacterial enzymes and to utilize metabolic pathways not used by normal cells. Findings of recombinant genetic studies have potential applications in medicine for correction of genetic defects and other problems. (49 Refs) (In GER)

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CLINICAL STUDIES OF CHROMOSOMES IN HUMAN CANCER

1. RESULTS OF INTENSIVE TREATMENT OF CHRONIC MYELOGENOUS LEUKEMIA.

Clarkson B
Memorial Sloan-Kettering Cancer Center, New York, NY
Nippon Ketsueki Gakkai Zasshi; 44(7):1263-1276 1981

Results of some cytokinetic studies in chronic myelogenous leukemia (CML) and recent attempts to alter the natural course of the disease are summarized. Patients treated with a single large dose of splenic radiation (800 rad) responded with only minor effect, but 6 wk later the same total dose given in eight fractions over a 3-wk period caused much greater and longer lasting reduction in WBC and spleen size. Fractionated irradiation of large amounts of bone marrow were also carried out to determine if similar effects would occur. Of 37 patients with typical Philadelphia chromosome positive (Ph'+) CML who were studied, 12 had significant reduction in the proportion of cells in the marrow containing the Ph' chromosome to less than one third of the initial values. In seven, no Ph'+ metaphases were found in the marrow. The absence of Ph'+ cells lasted only one to several mo in most, and only two patients had sustained reduction for over 3 yr. Median survival rate of the 37 patients was 50 mo; that of non-responders was 34 mo, while survival rate of 12 responders was approx 7 yr. The L-15 protocol was completed by 28 patients: splenic irradiation or hydroxyurea to control the leukocyte and platelet count, splenectomy, and combination therapy for remission induction with daunorubicin, cytosine arabinoside by continuous infusion, and 6-thioguanine. In 12/15 responders, all of the marrow metaphases found on direct chromosome preparations were entirely Ph' negative. The remissions were only temporary. (27 Refs)

2. 9;22;15 COMPLEX TRANSLOCATION IN PH1 CHROMOSOME POSITIVE CML REVEALED BY GIEMSA-11 PROCEDURE IN APPARENT LYMPHOID CELLS OF BLASTIC CRISIS.

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Cancer Genet Cytogenet; 4(4):283-292 1981

A Ph1 chromosome positive chronic myeloid leukemia patient whose chronic phase lasted 7.5 yr experienced a blastic transformation originating in the spleen. The spleen was infiltrated with undifferentiated blast cells that on cytogenetic analysis had a hyperdiploid karyotype and were Ph1 chromosome positive. The blast cells were negative for PAS, peroxidase, Sudan black and esterase stains. They were non-T, non-B with TdT activity. Remission was achieved in response to prednisone, vincristine, and adriamycin. Ph1 positive cells were present with cells responding to PHA stimulation throughout the course of the disease. A Giemsa-11 staining procedure made possible the ascertainment of a No 9 translocation chromosome in blastic crisis cells that had also been present in Ph1 chromosome positive cells early in the disease. The presence of this translocation initially in myeloid cells and subsequently in apparent lymphoid cell types suggests the origin of this patient's leukemia as a pluripotential stem cell. (Author abstract) (16 Refs)

3. HYPERCALCEMIA IN CHRONIC MYELOID LEUKEMIA.

Weiss Z, Plato A, Cohen D
Dept. Internal Medicine, Valley Medical Center, Afula, Israel
Harefuah; 101(3):63-64,91 1981

Hypercalcemia is commonly associated with solid tumors of the breast, lungs, and kidneys. It occurs in only 2.5-4.5% of patients with leukemia, usually those with acute lymphocytic leukemia (ALL). It is exceedingly rare in chronic myeloid leukemia (CML). The case of a 67-yr-old man with a 5 yr history of CML (with positive Philadelphia chromosome) who presented with complaints of low back pain, weakness, and weight loss and was found to have hypercalcemia in the range 12-14 mg/deciliter is reported. The patient had a low normal parathyroid hormone level, normal thyroid function, and normal prostaglandin level. Bone x-rays and a bone scan were negative. The WBC count was in the range 15,000-30,000/cc; the patient was not undergoing a blast crisis. Despite symptomatic treatment with saline, diuretics, and steroids as well as chemotherapy with busulfan and hydroxyurea, the patient continued to manifest hypercalcemia and hyperphosphatemia. The various mechanisms of hypercalcemia in malignant disease are discussed; hypercalcemia in the patient was attributed to probable marrow invasion. No autopsy or bone marrow biopsy was available to confirm the hypothesis. (17 Refs) (In HEB)

4. T LYMPHOID INVOLVEMENT IN B CELL NEOPLASMS AND MYELOID LEUKEMIA (MEETING ABSTRACT).

Nogueira Costa R, Spitzer G, Davis F, Kusyk C
M.D. Anderson Hospital and Tumor Institute, Houston, TX
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

T cell colonies (TCC) probably represent a subset of T+/-pre-T cells. We investigated if T cell involvement in hematological malignancies considered not to involve T cells could be demonstrated by cloning TCC. TCC were cloned from lymph nodes in cases of lymphoma and subacute myeloid leukemia, pleural effusions from lymphoma, blood, and marrow from acute myelogeneous leukemia (AML). To clone TCC, we used conditioned media prepared from nonadherent E rosette positive cells with 1% V/V phytohemagglutinin (PHA) HA15. As a marker for malignancy of the colonies, we measured nucleolar antigen and in some instances, cytogenetics. TCC were grown from histologically normal nodes from surgical operations, from nodes involved with non hematological neoplasms, and normal blood, marrow, and spleen. In all instances, nucleolar antigen was negative and in two instances, when studied, normal metaphases were obtained. T lymphoid involvement was also studied in a node of a subacute myeloid leukemia with nodal involvement and the marrow of two patients with acute myeloid leukemia. Nodal TCC were again positive for nucleolar antigen and contained 47 chromosomes, identical to the marrow cytogenetic abnormality. TCC grown from the marrow of the AML patients were also positive for nucleolar antigens. These studies suggest that there are abnormalities of the T cell lineage in B cell lymphomas of an indolent nature and in a certain proportion of patients with mye logeneous leukemia. (no Refs)

5. CYTOGENETIC STUDIES IN ADULT ACUTE LEUKEMIAS.

Takeuchi J, Ohshima T, Amaki I
Dept. Genetics and Endocrinology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Cancer Genet Cytogenet; 4(4):293-302 1981

Thirty-six patients with acute leukemia (31 with AML, 5 with ALL) were classified by FAB criteria, and their bone marrow cells were analyzed cytogenetically with G-banding. Chromosomal abnormalities were found in 16 patients (44%). The most common abnormality was an 8;21 translocation, accounting for 19.4% of all AML patients, that was restricted to patients with M2. In 29 treated AML patients, those with an 8;21 translocation [t(8;21) patients] showed a higher complete remission rate (83%) and a longer median survival (10.7 mo) than did other patients with AML; patients with only abnormal metaphases (AA patients) had the lowest complete remission rate (33%) and shortest median survival (2.7 mo). There was no difference in the remission rate and the survival between patients with only normal metaphases (N patients) and patients with abnormal metaphases (A patients). Three out of five patients with ALL had karyotypic abnormalities; the Philadelphia (Ph1) chromosome was found in one case. (Author abstract) (31 Refs)

6. FEATURES OF CHROMOSOMAL ABNORMALITIES IN ATYPICAL LEUKEMIA.

Tagawa M, Tomonaga Y
Dept. Hematology, Atomic Disease Inst., Nagasaki Univ. Sch. Medicine, Nagasaki, Japan
Rinsho Ketsueki; 22(6):789-791 1981

Bone marrow cells from 13 patients with atypical leukemia were studied cytogenetically using the banding technic. Chromosomal abnormalities were observed in three patients: missing Y, t(8;21), or 5p-with multiple change. Abnormal and normal diploid cells coexisted in all three patients. Cellular aging might have resulted in the loss of the Y chromosome. Clonal evolution of the karyotype could not be seen in 11 patients for whom serial cytogenetic analyses were obtained. (6 Refs) (In JPN)

7. CYTOLOGIC CHARACTERIZATION AND SIGNIFICANCE OF NORMAL KARYOTYPES IN T(8;21) ACUTE MYELOBLASTIC LEUKEMIA.

Berger R, Bernheim A, Daniel MT, Valensi F, Sigaux F, Flandrin G
Laboratoire de Cytogenetique, Centre Hayem, Hopital Saint-Louis, 2 Place du Dr. Fournier, 75475 Paris Cedex 10, France
Blood; 59(1):171-178 1982

A cytologic and cytogenetic study of 10 cases of acute myeloblastic leukemia with maturation and t(8;21) translocation is reported. Despite a certain polymorphic appearance, the characteristic cytologic picture, consisting essentially of large myeloblasts with an abundant cytoplasm containing a large Auer rod, allowed the presence of the chromosome anomaly to be predicted. t(8;21) translocation was attended by the loss of a sex chromosome in 7 of 10 cases. The comparative study of mitoses using cytologic and cytogenetic techniques showed that cells exhibiting normal karyotypes were essentially erythroblasts. This finding suggests that the chromosome anomaly does not affect all the bone marrow cell lines. After short-term culture, the percentage of normal karyotype mitoses diminished, as did the number of mitoses in erythroblasts. (Author abstract) (23 Refs)

8. TRANSLOCATION 4;11 IN ACUTE LYMPHOBLASTIC LEUKEMIA: CLINICAL CHARACTERISTICS AND PROGNOSTIC SIGNIFICANCE.

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Univ. Minnesota Hosp., Box 151 Mayo Memorial Building, Minneapolis, MN, 55455
Blood; 59(1):96-99 1982

Banded bone marrow chromosome analyses have been done on 83 unselected patients with acute lymphoblastic leukemia (ALL). Seven patients, all with non-T, non-B ALL, had a translocation involving the long arms of chromosomes 4 and 11. Five of these patients, four children and one adult, were first studied at diagnosis, and the t(4;11) (q21;q23) was the only karyotypic abnormality. All five presented with a marked leukocytosis (greater than 150 x 10(9)/liter). Four of these five patients achieved a complete remission following the same intensive treatment regimen; however, remission duration and survival were very short (medians 2.5 and 8 mo respectively). The fifth patient is currently receiving induction chemotherapy. The remaining two patients, both adults, were studied in relapse only, and had other karyotypic abnormalities in addition to the t(4;11). One of these relapse patients was a female whose clinical presentation and course were similar to those above. The last patient was a male who presented with a leukocyte count of 7 x 10(9)/liter and maintained an initial complete remission for 37 mo. Our data suggest that patients who have a t(4;11) (q21;q23) at the time of diagnosis of ALL have a poor prognosis with conventional therapy and require a new therapeutic approach. (Author abstract) (11 Refs)

9. METHODS OF PROCESSING MARROW SAMPLES MAY AFFECT THE FREQUENCY OF DETECTABLE ANEUPLOID CELLS.

Waghray M, Eques C, Rowley JD, Martin P, Testa JR
(c/o Rowley) Dept. Medicine, Univ. Chicago, Box 420, 950 East 59th St., Chicago, IL, 60637
Am J Hematol; 11(4):409-415 1981

Karyotypes were analyzed from 14 patients with various myeloproliferative disorders who had marrow samples processed directly and cultured in various ways. Eleven patients had acute nonlymphocytic leukemia (ANLL) (7 patients) or a dysmyelopoietic syndrome (4 patients). All of these patients were known to have an abnormal karyotype, and in each case, two samples of a bone marrow aspirate were available: one processed directly and another cultured for 24 hr. Five of the 11 patients had essentially the same proportion of abnormal cells in the direct and 24-hr samples; in five other patients, the percentage of aneuploid cells in the sample cultured for 24 hr was higher than that in the direct preparation. A higher percentage of aneuploid cells was observed in the direct preparation in only one case. In three other cases of ANLL, a marrow aspirate was cultured with methotrexate in addition to samples processed directly and after 24-hr culture; only two of these had an abnormal clone in any sample. The results of karyotype analysis differed in these two patients. The proportion of aneuploid cells was substantially higher in the methotrexate culture than in the 24-hr culture in one patient; in the other patient, the 24-hr culture contained aneuploid cells, whereas the methotrexate culture showed none. Three of the 13 aneuploid patients would have been incorrectly classified as being karyotypically normal on the basis of the initial analysis of the direct preparation, since only a single abnormal cell was detected in each case. The karyotypic pattern in untreated patients with ANLL has prognostic significance; therefore, the method of processing marrow aspirates may substantially influence the degree of correlation between the karyotype and survival reported by different laboratories. (Author abstract) (11 Refs)

10. GAMMA (IMMUNE) INTERFERON PRODUCTION BY LEUKOCYTES FROM A PATIENT WITH A TG CELL PROLIFERATIVE DISEASE.

Hooks JJ, Haynes BF, Detrick-Hooks B, Diehl LF, Gerrard TL, Fauci AS
NIDR, NIH, Building 10, Room 2B19, Bethesda, MD, 20205
Blood; 59(1):198-201 1982

We report a patient with a disease characterized by proliferation of T cells with Fc receptors for IgG (TG). However, unlike lymphoid cells from normal individuals or from patients with other lymphoid malignancies, the patient's lymphocytes spontaneously produced gamma interferon (IFN-gamma) in vitro. The peripheral lymphocytes consisted of 95% TG cells, which exhibited the morphological characteristics of T-cell chronic lymphocytic leukemia (CLL) and were normal on cytochemical and chromosome analysis. The majority of TG cells were OKT3+, OKT8+, and OKT4-, 3A1-. These cells failed to express suppressor cell activity and displayed depressed levels of natural killer activity, but mediated antibody-dependent cell-mediated cytotoxicity. The spontaneous production of IFN-gamma by human peripheral lymphoid cells as demonstrated in this study may serve as a probe for studying the relationship between IFN-gamma and the proliferation of human T-cell subsets. (Author abstract) (16 Refs)

11. CLONAL CHARACTERISTICS OF CUTANEOUS T CELL LYMPHOMAS: CYTOGENETIC EVIDENCE FROM BLOOD, LYMPH NODES, AND SKIN.

Nowell PC, Finan JB, Vonderheid EC
Dept. Pathology/G3, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
J Invest Dermatol; 78(1):69-75 1982

Chromosome studies were done on mitogen-stimulated lymphocytes from one or more tissues (blood, lymph nodes, skin lesions) in 15 patients with mycosis fungoides or Sezary syndrome. A cytogenetically abnormal clone was found in 10 individuals, including 6 with data from several tissues. In four cases the same aberrant clone was identified in a skin lesion as well as in blood and/or lymph node. the abnormal chromosome patterns ranged from hypodiploid to hypertetraploid, and there was no evidence of unrelated karyotypically-altered lines at different sites. A 6q- chromosome, previously reported in acute lymphocytic leukemia, was found in two patients. The results support the concept that cutaneous T cell lymphomas (CTCL) are clonal disorders, presumably unifocal in origin, with the skin lesions populated by cells from the same neoplastic clone that involves lymph nodes and blood. (Author abstract) (17 Refs)

12. THREE PATIENTS WITH STRUCTURALLY ABNORMAL X CHROMOSOMES, EACH WITH XQ13 BREAKPOINTS AND A HISTORY OF IDIOPATHIC ACQUIRED SIDEROBLASTIC ANEMIA.

Dewald GW, Pierre RV, Phyliky RL
Mayo Clinic, Rochester, MN, 55905
Blood; 59(1):100-105 1982

Structural abnormalities of the X chromosome are rarely found in neoplastic disorders. We describe three patients with a history of idiopathic acquired sideroblastic anemia (IASA); each one had an abnormal clone of cells in the bone marrow, characterized by a structurally abnormal X chromosome. In two of these patients, the predominant karyotype was 47,X,2idic(X)(q13); in the other patient, it was 46,X,t(X;11)(q13;p15). Inasmuch as all three of these cases involved chromosome band Xq13, as did two previously published cases, we suggest that band Xq13 may be more prone to structural rearrangement than other X chromosome bands in hematologic disorders. The common Xq13 chromosome breakpoint and clinical presentation (IASA) among these three patients and the occurrence of an X-linked type of sideroblastic anemia may suggest that an association exists between X chromosome abnormalities and IASA. Perhaps alteration of a gene or chromosome structure in or near band Xq13 predisposes to development of IASA. The fact that two of these patients had preleukemia and the third had overt acute leukemia may imply that patients with IASA and X chromosome abnormalities have a poor prognosis. Cases of IASA without associated X chromosome abnormalities are known; thus, if an association between IASA and an abnormal X chromosome does exist, most likely it involves only some patients with IASA. (Author abstract) (22 Refs)

13. ANALYSIS OF THE ANDROGEN RESPONSE OF 23 PATIENTS WITH AGNOGENIC MYELOID METAPLASIA: THE VALUE OF CHROMOSOMAL STUDIES IN PREDICTING RESPONSE AND SURVIVAL.

Besa EC, Nowell PC, Geller NL, Gardner FH
Medical Coll. Pennsylvania, 3300 Henry Ave., Philadelphia, PA, 19129
Cancer; 49(2):308-313 1982

The responses of 23 patients with agnogenic myeloid metaplasia (AMM) to androgen therapy were studied. Various clinical and laboratory parameters were analyzed for their value in determining response to therapy and length of survival. Fifty-seven percent of patients responded, as determined by a sustained increase in hematocrit within 3 mo of therapy which thus eliminated the need for transfusions. Chromosome study of the abnormal hemic population was the best predictor of response: 92% of patients with normal chromosomes responded, while 78% of patients with chromosomal abnormalities did not. Responders had a mean survival time of 5 1/2 yr from the time of diagnosis as compared with 2 yr for the nonresponders. The degree of thrombocytopenia, suppression of the ferrokinetic, and lack of activity in axial skeleton on bone marrow scans indicated severly compromised hemopoiesis in the nonresponders. The results suggest that in some patients with AMM, more extensive cytogenetic alterations in the abnormal hematopoietic cells result in an inability to respond to androgen therapy and that the chromosome study is the test most accurate for predicting the outcome of therapy. (Author abstract) (29 Refs)

14. ERYTHROLEUKEMIA AND OTHER HEMATOLOGIC COMPLICATIONS OF INTENSIVE THERAPY IN LONG-TERM SURVIVORS OF SMALL CELL LUNG CANCER.

Bradley EC, Schechter GP, Matthews MJ, Whang-Peng J, Cohen MH, Bunn PA, Ihde DC, Minna JD
Dept. Medicine, Beth Israel Hosp., Boston, MA
Cancer; 49(2):221-223 1982

Eight patients with small cell bronchogenic carcinoma treated with intensive combination chemotherapy, with and without radiotherapy, have been followed for a minimum of 2 1/2 yr without relapse. One patient, after a prodrome of macrocytic sideroblastic anemia, leukopenia, and thrombocytopenia, experienced erythroleukemia 34 mo after starting chemotherapy, and cytogenetic studies revealed extensive chromosomal abnormalities. Another patient had persistent macrocytic anemia and pancytopenia 2 yr after cessation of therapy. The remaining six patients have normal peripheral blood smears and cell counts. A significant incidence of preleukemic syndromes and acute leukemia appearing as late complications in intensively treated small cell lung cancer patients requires confirmation in larger series of long-term survivors. Prospective determination of marrow karyotype abnormalities may help to identify patients at greatest risk for developing secondary leukemia. (Author abstract) (13 Refs)

15. CONSTITUTIVE HETEROCHROMATIN (C-BANDING) STUDIES IN PATIENTS WITH TESTICULAR MALIGNANCIES.

Robson MK, Anderson JM, Garson OM, Matthews JP, Sandeman TF
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Cancer Genet Cytogenet; 4(4):319-323 1981

The heterochromatic index [qh/(p + q) x 100] is a quantitative measure of variations in the heterochromatic regions of C-banded cells which minimizes differential contraction of heterochromatic and euchromatic areas. Heterochromatic indices of the homologues of chromosomes number 1, number 9, number 16, and Y were studied in the genotypes of 48 patients with germinal tumors and in 30 controls. The heterochromatic indices of chromosome number 9 in patients showed statistically significant heteromorphism compared with controls. In addition, the heteromorphism was found to increase from the lower malignancy seminoma to the highly malignant teratoma. A similar but statistically nonsignificant pattern was seen in chromosome number 16. No statistical difference in the mean of the heterochromatic indices was found in chromosomes number 1 and Y. The difference in the mean heterochromatic index in chromosome number 9 appeared to be due to an increase in the amount of constitutive heterochromatin and not to a decrease. (Author abstract) (12 Refs)

16. COMBINED CELL SURFACE ANTIGENS AND CHROMOSOMAL STUDIES IN BLADDER CANCER.

Javadpour N, Roy JB, Bottomley R, Dagg K
Surgery Branch, NCI, Bethesda, MD, 20205
Urology; 19(1):29-32 1982

The conventional histopathologic examination of a primary tumor does not predict the potentiality for invasiveness and recurrence of a superficial low-grade transitional cell carcinoma of the bladder. We have utilized combined cell surface antigens and chromosomal analysis to predict the natural history of the bladder cancer in 20 patients in a double blind study. In this preliminary report it appears that both cell surface antigens and chromosomal abnormalities correlate well with the stages and grades of bladder cancer. (Author abstract) (12 Refs)

DNA CONTENT AND PLOIDY CHANGES ASSOCIATED WITH CANCER

17. NUCLEAR DNA MODAL PATTERNS AS DIAGNOSTIC CRITERIA IN HUMAN LUNG CANCER.

Ozaki HS, Yoneyama T, Eguchi K, Kodama T, Hoshino K
Dept. Anatomy, Faculty Medicine, Kyoto Univ., Sakyo-ku, Kyoto 606, Japan
Jpn J Clin Oncol; 11(3):431-441 1981

Nuclear DNA content distributions from 76 lung tumor samples obtained from 70 patients were divided into types by analysis of modal values calculated with logarithmically transformed data. Cytofluorometry was used to measure DNA contents in samples from 48 adenocarcinomas, 14 squamous cell carcinomas, 4 adenosquamous carcinomas, 5 large cell carcinomas, 2 small cell carcinomas, 2 carcinoids, and 1 mucoepidermoid carcinoma. The nuclear DNA distribution histograms could be separated by modal values into three major types: I, diploid-tetraploid (27/70 patients); II, triploid (34/70 patients); and III, mixed (9/70 patients), with six, four, and four subtypes, respectively. The most frequent DNA histogram subtype was all triploid (Type IIA, 19/70 patients), which is in agreement with other reports. In five patients the major type was the same in the primary tumor and metastatic tumor found at the same time. One patient had a distribution pattern in the primary tumor (IIA) that differed from that in its metastasis (IIB, 2 peaks, diploid + hexaploid), which developed later. Preliminary date suggest that degree of malignancy and prognosis are related to type of nuclear DNA Content distribution in the tumor. (22 Refs)

18. DNA CONTENT OF CONDYLOMA ACUMINATUM.

Shevchuk MM, Richart RM
Div. Uropathology, Columbia Univ., 630 West 168th St., New York, NY, 10032
Cancer; 49(3):489-492 1982

Female genital condylomata acuminata were examined for DNA content. Diploid and polyploid DNA distributions, including tetraploidy and octaploidy, were found. These findings are in clear counterdistinction to squamous intraepithelial lesions, which have been found to be aneuploid. DNA quantitation, therefore, can be used in difficult cases to distinguish between condylomatous and neoplastic epithelium. (Author abstract) (21 Refs)

19. COMPARATIVE STUDY ON THE NUCLEAR DNA CONTENT OF LEIOMYOMA, LEIOMYOBLASTOMA AND LEIOMYOSARCOMA OF THE STOMACH AND SMALL INTESTINE.

Kimura O, Kaibara N, Tamura H, Nishidoi H, Okamoto T, Koga S
(c/o Kaibara) The 1st Dept. Surgery, Tottori Univ. Sch. Medicine, 36-1-Nishimachi, Yonago 683, Japan
Jpn J Surg; 11(6):428-432 1981

Nuclear DNA contents in tumor cells of leiomyoma (LM), leiomyoblastoma (LB) and leiomyosarcoma (LS) of the stomach and small intestine were determined and the DNA distribution pattern and histopathological findings were evaluated. Five LM, four LB, and two LS of the stomach, and one LS of the small intestine were obtained at the time of gastrectomy, intestinal resection and biopsy. Nuclear DNA content was determined by staining the sections according to the Feulgen method. Three of five gastric LM had developed in the gastric corpus and two were located in the cardia. No ulcer formation of LM, except in one case, was noted. LB were located in the corpus and cardia. Ulcer formation was noted in two patients. LS were the largest in size, and ulcer formations were apparent in all patients. The mean DNA content for LM was 2.2-2.7 CC (CC= range distribution), 3.0-3.1 CC for LB, and 4.6-5.8 CC for LS. Peak DNA values were in the diploid area in LM and LB. Missing of peak value in LS indicated aneuploidy. A significant difference in nuclear DNA content exists among the tumors, and percentage of nuclei with DNA content 3 or 4x over the basic CC represent good indices for distinguishing between benign and malignant conditions. In differentiated types of LS is sometimes difficult to make histopathological distinction between LM and LB. Diagnosis of LS may be more accurate when more than 80% of the nuclei have DNA content values greater than 3x of basic nuclear content and when more than 50% exhibit values greater than 4x of basic content. (8 Refs)

20. CELL-KINETIC AND GENETIC CHARACTERIZATION OF SQUAMOUS EPITHELIAL CARCINOMAS OF THE HEAD AND NECK.

Muller RP, Addicks HW, Gohde W, Schumann J
Radiologische Klinik der Universitat, Jungeblodtplatz 1, D-4400 Munster, W. Germany
Dtsch Zahnaerztl Z; 36(11):693-696 1981

Analysis of epithelial carcinomas of the head and neck by impulse cytophotometry (IC) is described. Tumor tissues samples obtained by excision or needle biopsy are worked up immediately after removal; samples may be fresh or fixed in 70% methanol or ethanol. Results can be obtained within 10-15 min after removal of the sample from the patient. IC produces a histogram containing information about ploidy stages of cells in the sample. The mean chromosome number for the sample is calculated using a computer program. From IC the proliferative activity of the sample, indicated by the fraction of cells in the S-phase, is determined. Normal tissue consists mainly of diploid cells; the fraction of normal cells with higher DNA content usually does not exceed 10%. Various tumor types such as melanoma, squamous epithelial carcinoma, testicular tumors, and sarcomas are aneuploid in 80-100% of cases. S-phase cells in tumor tissue can account for as much as 25% of the total cell population (up to 50% for solid tumors). Although data for in vivo tumors are not available, evidence indicates that the radiosensitivity of tumors is related to proliferative activity. Thus IC provides a quick method for determining tumor radiosensitivity for a minimal expenditure of time and money. (14 Refs) (In GER)

21. VULVAR INTRAEPITHELIAL NEOPLASIA: CORRELATION OF NUCLEAR DNA CONTENT AND THE PRESENCE OF A HUMAN PAPILLOMA VIRUS (HPV) STRUCTURAL ANTIGEN.

Crum CP, Braun LA, Shah KV, Fu YS, Levine RU, Fenoglio CM, Richart RM, Townsend DE
Div. Ob/Gyn Pathology, Columbia Univ. Coll. of Physicians and Surgeons, 630 West 168th St., New York, NY, 10032
Cancer; 49(3):468-471 1982

Immunoperoxidase localization of a human papilloma virus structural antigen (HPV) was attempted in 68 intraepithelial lesions of the vulva, 39 of which were analyzed for nuclear DNA content by microspectrophotometry. Overall, 5.9% (4/68) stained positive for HPV. Ninety per cent (35/39) of the cases tested were aneuploid, and, of these, 2.8% (1/35) stained positive for HPV. In contrast, 50% (2/4) of the polyploid lesions were positive. Hence DNA microspectrophotometry and immunoperoxidase localization of HPV are useful coparameters for distinguishing wart virus infection (condylomata) from vulvar intraepithelial neoplasia. HPV is detected infrequently within aneuploid lesions, in keeping with the concept that epithelial maturation is required for virion assembly. Whether the HPV genome exists in a nonreplicative state within the aneuploid cell population is unknown. (Author abstract) (18 Refs)

22. CLASSIFICATION OF THE MALIGNANCY OF CANCER BY ANALYSIS OF DNA IN THE CELL NUCLEI, TESTED IN CANCER OF THE STOMACH AND OF THE ESOPHAGUS (MEETING ABSTRACT).

Sannohe Y
Second Dept. Surgery, Sch. Medicine, Fukuoka Univ., Nishi-ku, Fukuoka 814, Japan
Nippon Shokaki Geka Gakkai Zasshi; 14(6):743 1981

The nuclear DNA content of surgical specimens of esophageal cancer from 40 patients and of stomach cancer from 100 patients was determined by fluorescent microspectrophotometry. The histogram patterns of DNA obtained were compared with the histopathological findings of hematoxylin and eosin-stained specimens, such as the relationship to clinical diagnosis, precancerous changes, equivalency of treatment and prognosis. Cell malignancy or nonmalignancy was diagnosed by the following cell chromosome features: hypotriploid in less than 15%, triploidy in less than 5% and quadriploidy in less than 5% were considered benign and hypotriploid in more than 20%, triploidy in more than 10% and quadriploidy in more than 5% were considered malignant. In the prognostic evaluation of stomach cancer, DNA histogram pattern Type I was defined as the superficial spreading type and histogram pattern Type IV was accompanied by lymphatic invasion or hepatic metastasis and the prognosis was poor. In esophageal cancer, the prognosis was mostly good. (no Refs) (In JPN)

23. CELLULAR DNA CONTENT OF PITUITARY TUMOURS: ITS RELATIONSHIP TO MORPHOLOGY AND HORMONAL TYPE OF TUMOUR.

Anniko M, Holm LE, Silfversward C, Tribukait B, Wersall J
Dept. Otolaryngology, Karolinska Hosp., S-104 01 Stockholm, Sweden
Acta Otolaryngol [Suppl] (Stockh); (379):13-19 1981

The DNA content of 24 human pituitary tumors was analyzed with flow-cytofluorometry, and compared with the morphologic characteristics of the tumors. Fifteen tumors had a diploid and 9 had an aneuploid DNA pattern. Minimal and moderate degrees of mitosis and nuclear polymorphism can possibly occur more frequently in aneuploid pituitary tumors than in diploid pituitary tumors (mitoses: 56% vs 27%; nuclear polymorphism: 78% vs 53%). Otherwise no correlation between the degree of ploidy and the histopathologic or ultrastructural features could be registered. Thus, pituitary tumors of the same morphology can be subdivided according to their ploidy pattern. (Author abstract) (17 Refs)

24. THE CLINICAL IMPLICATIONS OF DNA CHARACTERISTICS IN HUMAN PITUITARY TUMOUR DISEASE.

Anniko M, Holm LE, Tribukait B, Werner S, Wersall J
Dept. Otolaryngology, Karolinska Hosp., S-104 01 Stockholm, Sweden
Acta Otolaryngol [Suppl] (Stockh); (379):21-28 1981

DNA analysis was performed in 29 cases of various endocrinological types of huma n pituitary tumors. The degrees of ploidy and proliferation, expressed as the proportion of cells in S phase, were determined. In 12 cases (41%) aneuploidy occurred. The proportion of aneuploid cells in these tumors was very high, in general around 95% measured. The aneuploid group of pituitary tumors showed a large variation of the percentage of cells in S-phase (range: 3.3-13.7%; mean: 8.3 +-5.3) in contrast to diploid tumors which showed a considerably smaller variation (range: 3.4-8.8%; mean 5.5 +-2.1). Patients with aneuploid tumors had a mean age at operation of 42.8 +-11.1 yr in contrast to 51.5 +-13.8 yr for patients with diploid tumors. Aneuploidy occurred more frequently in tumors causing acromegaly with a concomitant secretion of GH and PRL than in other endocrinological types of tumors. Patients with aneuploid tumors had a mean case history of 2.9 +-1.9 yr, as compared to 10.5 +-4.9 yr for patients with diploid tumors. In many cases, tumors with an aneuploid DNA pattern caused a high clinical activity of acromegaly. (Author abstract) (28 Refs)

25. DNA CHARACTERISTICS OF HUMAN PITUITARY TUMOURS.

Anniko M, Holm LE, Tribukait B, Werner S
Dept. Otolaryngology, Karolinska Hosp., S-104 01 Stockholm, Sweden
Acta Otolaryngol [Suppl] (Stockh); (379):5-11 1981

Biopsies from pituitary tumors in eight patients were analyzed with DNA flow-cytofluorometry immediately after surgery and after organ culture. Good agreement was found between the degrees of ploidy and of the relative proportions of cells in different phases of the cell cycle, indicating a good stability and reproducibility of pituitary tumor explants in vitro. Analysis of DNA content indicated a homogeneous cell population in tumors before and after explanation. No apparent correlation was observed between hormone secretion rate in diploid and aneuploid tumors, respectively, and DNA characteristics. (Author abstract) (19 Refs)

26. CLINICOPATHOLOGICAL STUDIES OF DNA CONTENT IN NUCLEI OF CELLS ISOLATED FROM PATIENTS WITH ESOPHAGEAL CARCINOMA.

Hiratsuka R
Second Dept. Surgery, Sch. Medicine, Fukuoka Univ., Fukuoka 812, Japan
Fukuoka Igaku Zasshi; 72(10):556-574 1981

Nuclear DNA content in cells from 37 patients with esophageal cancer was measured by means of microfluorometry and Feulgen staining. Patients were divided into four groups according to DNA histogram patterns: Type I (7 patients) had cells that were generally hypotriploid, with less than 30% hypertetraploid. Type II (7 patients) had cells between diploid and tetraploid, with greater than 30% hypertetraploid. Type III (12 patients) had cells in the tetraploid-hexaploid range, with less than 60% greater than tetraploid. Type IV (12 patients) had cells in the tetraploid-hexaploid range, with greater than 60% greater than tetraploid. Poorly differentiated squamous cell carcinoma occurred in 5/12 Type IV patients but not an any Type I patients. Lymphatic permeation occurred in 1/7 Type I and 7/12 Type IV patients. Marked lymphatic metastasis occurred in 4/7 Type I and 11/12 Type IV patients. Survival time was greater than 3 yr for 4/5 Type I patients but less than 1 yr for 7/11 Type IV patients, who died of recurrent cancer. Biopsy specimens from 15/26 recurrent tumors had the same DNA histogram patterns as the original tumors. Because unusual characteristics make morphological staging alone inadequate for prognosis of gastric cancer, evaluation of DNA content is recommended in conjunction with staging. (39 Refs) (In JPN)

27. CYTOPHOTOMETRIC ANALYSIS OF HUMAN CHORIOEPITHELIOMAS, MELANOMA, EWING'S SARCOMA, AND MAMMARY GLAND CARCINOMA TRANSPLANTED INTO ATHYMIC MICE. COMMUNICATION II.

Revazova ES, Petrova AS, Zubrikhina GN, Iudicheva TN
All-Union Cancer Res. Center, Moscow, USSR
Lab Delo; (11):668-669 1981

DNA content was studied in cells of human melanoma, Ewing's sarcoma, breast carcinoma, and chorioepithelioma transplanted into athymic mice. Pulse cytophotometric analysis showed the monomodal distribution of ploidy in Ewing's sarcoma cells; greater than 50% of cells had diploid DNA content. Majority of melanoma cells had triploid and tetraploid DNA content, while diploid cells comprised only 6.1% of cell population. Chorioepithelioma and breast carcinoma cells were characterized be marked heterogeneity. (3 Refs) (In RUS)

28. FLOW CYTOMETRIC ANALYSIS OF THE RESPONSE OF THE R3327-G RAT PROSTATIC ADENOCARCINOMA TO ENDOCRINE MANIPULATION.

Pollack A, Bagwell CB, Block NL, Irvin GL, Claflin AJ, Stover BJ
Res. Service 151, Veterans Admin. Medical Center, 1201 NW 16 St., Miami, FL, 33125
J Surg Oncol; 18(4):389-398 1981

The technique of flow cytometric DNA histogram analysis (FCM) shows there to be two distinct cell populations (diploid vs aneuploid) in the poorly differentiated R3327-G rat prostatic adenocarcinoma. The following study compares tumor wt measurements with several FCM computer-based methods designed to determine rapidly the proliferative status of tumors. Hypophysectomy, bilateral adrenalectomy, orchiectomy, sham operations, or diethylstilbestrol treatments were initiated when the tumors were palpable (day 21) and continued until the tumors were excised (day 52). Hypophysectomy, orchiectomy, adrenalectomy, and diethylstilbestrol treatments all resulted in significant inhibition by tumor wt. Quantitation of the percentage of mid-S phase aneuploid cells by summation gave the best correlation with tumor wt. Tumors grown in hypophysectomized, orchiectomized, adrenalectomized, or diethylstilbestrol-treated animals showed a significant reduction in the proportion of mid-S phase cells as compared with controls. The calculation of the percentage of all aneuploid cells was significantly reduced in hypophysectomy, orchiectomy, and diethylstilbestrol-treated animals. However, tumors grown in adrenalectomized animals were not significantly different from controls by this method. Adrenalectomy was found to be the least effective form of therapy, and this was reflected in all of the parameters measured. These data show that FCM analysis may be useful in the quantitation of prostatic carcinoma response to therapy. (Author abstract) (34 Refs)

29. EFFECT OF ANTINEOPLASTIC ANTIBIOTIC ACTINOXANTHINE ON CELLS GROWING IN VITRO.

Borodina VM, Kir'ianova EA, Zelenin AV, Reshetov PD, Chupova LA
Inst. Molecular Biology, Moscow, USSR
Antibiotiki; 26(12):915-919 1981

Biological activity of antineoplastic antibiotic actinoxanthine (AX) was studied in cultured murine L fibroblasts. Cells growing in a monolayer were treated with AX at 1-50 ug/ml. Fluorescence microscopy showed marked changes in the cell nuclei (formation of chromatin bodies, shifting of chromatin bodies towards the nuclear membrane, decrease of the number of nucleoli). The changes in the morphology of cell nuclei depended upon the AX concentration and the duration of exposure. Cytofluorimetric analysis showed a 40% decrease of DNA synthesis in cells treated with AX. Autoradiography showed a 70-80% inhibition of RNA synthesis. AX at 50 ug/ml caused complete inhibition of mitotic activity. AX did not affect the cell membranes of lysosomal membranes. (16 Refs) (In RUS)

CHROMOSOMAL FRAGILITY AND GENETIC FACTORS PREDISPOSING TO HUMAN CANCER

30. THE MYELOPROLIFERATIVE REACTION IN A CHILD WITH DOWN SYNDROME: CYTOLOGICAL AND CHROMOSOMAL EVIDENCE FOR A TRANSIENT LEUKEMIA.

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Dept. Pediatrics, James Whitcomb Riley Hosp. for Children, 1100 W. Michigan St., Indianapolis, IN, 46223
Am J Hematol; 11(4):417-423 1981

Infants with Down syndrome occasionally develop marked myeloproliferative reactions (MPR) indistinguishable from acute myelocytic leukemia but which spontaneously regress. Most authors have attributed MPR to immature or defective control on bone marrow development. In this report serial cytomorphologic and chromosomal findings in the bone marrow and peripheral blood of a child with the MPR suggests that MPR may be due to a spontaneously regressing clone of malignant cells. At the height of the myeloproliferative response, chromosomal studies demonstrated a clone of blast-like cells with a 21-22 translocation consistent with Down Syndrome and an X-8 translocation which was present only in the initial peripheral blood analysis harvested at 24 hr but was not present in the 72 hr samples. This X-8 translocation was not demonstrated in bone marrow or peripheral blood samples obtained at random times throughout the 1 yr followu p. During this period there was complete resolution of the MPR. In addition the chromosomes from one cell demonstrated several double minutes at the time of the MPR. Double minutes have previously been reported only in malignant diseases, especially tumors of neural origin and leukemia. These findings raise questions about the benign origin of the MPR and support the idea the MPR may be the result of a spontaneously regressing clone of malignant cells. (Author abstract) (22 Refs)

31. CATALASE LEVELS IN PATIENTS WITH ANIRIDIA AND/OR WILMS' TUMOR: UTILITY AND LIMITATIONS.

Ferrell RE, Riccardi VM
Genetic Marker Lab., Univ. Texas Health Science Center at Houston, P.O. Box 20334, Houston, TX, 77025
Cytogenet Cell Genet; 31(2):120-123 1981

The gene for red blood cell (RBC) catalase has recently been mapped to 11p13 and a gene dosage effect has been demonstrated for individuals with triplication or deletion of that region. Deletion of the 11p13 band has also been associated with aniridia, with and without Wilms' tumor. We studied the RBC catalase levels in individuals without detectable chromosomal abnormalities but with aniridia, Wilms' tumor, and the combination of aniridia and Wilm's tumor, to determine whether catalase levels might provide evidence for a sub-microscopic chromosomal deletion in the 11p13 region. All karyotypically normal patients were found to have normal catalase levels. (Author abstract) (14 Refs)

32. DELINEATION OF 13Q - DELETION BY REPLICATION BANDING IN RETINOBLASTOMA.

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Cytogenet Cell Genet; 31(2):77-83 1981

High-resolution replication banding was performed to (1) delineate at the prometaphase level small interstitial deletions of chromosome 13 in two unrelated patients with retinoblastoma (Rb) and (2) study the influence of these deletions in the replication autonomy of the regions involved. The present study indicates that, in spite of the fact that break points separate (split) bands q14 and q21 in different segments, these deletions do not produce a position effect or alteration in the replication behavior of the abnormal chromosome 13's. Each segment in the deleted chromosomes replicates with a chronology and pattern identical to the normal homolog's. The present data also indicate that metaphase bands are not only autonomous foci of replication but that they can be further divided into subunits of replication which correspond to sub-bands observed in more elongated prometaphase chromosomes. Our results strongly suggest that prometaphase sub-bands represent units of chromatid organization and replication. (Author abstract) (32 Refs)

33. RADIOSENSITIVITY OF FIBROBLASTS FROM PATIENTS WITH RETINOBLASTOMA AND CHROMOSOME-13 ANOMALIES.

Ejima Y, Sasaki MS, Utsumi H, Kaneko A, Tanooka H
Radiation Biology Center, Kyoto Univ., Yoshida-Konoecho, Sakyo-ku, Kyoto 606, Japan
Mutat Res; 103(2):177-184 1982

Cultured fibroblast strains were established from skin biopsies from 14 patients with retinoblastoma (RB) and 5 non-RB patients with inborn chromosome-13 anomalies, and their sensitivities to cell killing by x-rays were compared with those of similarly established cell lines from 7 normal, healthy (N) persons and a patient with ataxia telangiectasia (AT), which represented the radiosensitive reference strain. Cells grown in antibiotic and serum-supplemented alpha-modified minimal essential medium were subjected to a dose of 1,500 rad/min of soft x-rays, except the AT cells, which received 810 rad/min. The cells from the AT patient showed marked sensitivity compared to N cells, but those from RB patients exhibited no radiosensitivity. Cells from 4/5 sporadic RB cases in the sample actually showed resistance to x-ray. The cells of non-RB patients with chromosome-13 anomalies were slightly radiosensitive at lower x-ray doses, but otherwise were not more radiosensitive than N cells. Neither the radiosensitivity of RB nor the presence of a repair locus on chromosome-13 is supported by the present results. (26 Refs)

34. DNA DAMAGE AND ITS REPAIR IN HUMAN NORMAL OR XERODERMA PIGMENTOSUM FIBROBLASTS TREATED WITH 4-NITROQUINOLINE 1-OXIDE OR ITS 3-METHYL DERIVATIVE.

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Dept. Genetics, Univ. Coll. Swansea, Singleton Park, Swansea SA2 8PP, England
Carcinogenesis; 2(12):1359-1362 1981

Normal human or excision deficient xeroderma pigmentosum (XP) fibroblasts were exposed to either the potent carcinogen 4-nitroquinoline 1-oxide (4NQO) or the weaker acting 3 methyl derivative of this compound. The inhibition of cell growth, DNA damage and DNA repair were then monitored in these cells. The data indicate that the modification of 4NQO by methylation actually changes the type and amount of DNA damage induced by this carcinogen. More specifically, the methylation of 4NQO at the three position prevented the formation of 4NQO induced DNA adducts manifesting themselves as alkaline stable lesions whose repair was cytosine arabinoside inhibitable in normal cells, but defective in excision deficient XP cells. Alkaline labile lesions induced by 4NQO which are repairable in the above XP cells were still induced by the 3 methyl derivative but a lower frequency on an equimolar basis. (Author abstract) (13 Refs)

35. INVESTIGATION OF THE SISTER CHROMATID EXCHANGE (SCE) FREQUENCY IN ONE PATIENT WITH XERODERMA PIGMENTOSUM.

Went M, Szorenyi A, Polay A, Simon N
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Arch Dermatol Res; 271(4):407-409 1981

The sensitivity of xeroderma pigmentosum (XP) cells from one patient to chemical mutagens was studied as a potential cytogenetic test. When the phytohemagglutinin-stimulated XP lymphocytes were exposed to mitomycin C prior to their first division, an increased rate of sister chromatid exchange (SCE) was observed. The high rate of SCE is a measurement of the amount of non-excisible or non-excised damage and consequently shows the altered capability of cells to repair DNA damage by a variety of physical and chemical factors. (14 Refs)

36. INTERACTION OF HUMAN AND CHICK DNA REPAIR FUNCTIONS IN UV-IRRADIATED XERODERMA PIGMENTOSUM-CHICK ERYTHROCYTE HETEROKARYONS.

Bootsma D, Keijzer W, Van Der Veer E, Rainaldi G, De Weerd-Kastelein EA
Dept. Cell Biology and Genetics, Erasmus Univ. Rotterdam, 3000 DR Rotterdam, The Netherlands,
Exp Cell Res; 137(1):181-189 1982

Fusion of chick erythrocytes with human primary fibroblasts results in the formation of heterokaryons in which the inactive chick nuclei become reactivated. The expression of chick DNA repair functions was investigated by the analysis of the DNA repair capacity after exposure to ultraviolet (UV) irradiation of such heterokaryons obtained after fusion of chick erythrocytes with normal human or xeroderma pigmentosum (XP) cells of complementation groups A, B, C, and D. Unscheduled DNA synthesis (UDS) in normal human nuclei in these heterokaryons is suppressed during the first 2-4 days after fusion. The extent and duration of this suppression is positively correlated with the number of chick nuclei in the heterokaryons. Suppression is absent in heterokaryons obtained after fusion of chicken embryonic fibroblasts with XP cells (complementation group A and C). Restoration of DNA repair synthesis is found after fusion in XP nuclei of all complementation groups studied. It occurs rapidly in XP group A nuclei, starting one day after fusion and reaching near normal human levels after 5-8 days. In nuclei of the B, C and D group increased levels of UDS are found 5 days after fusion. At 8 days after fusion the UDS level is about 50% of that found in normal human nuclei. The pattern of UDS observed in the chick nuclei parallels that of the human counterpart in the fusion. A fast complementation pattern is also observed in chick fibroblast-XP group. A heterokaryons resulting within 24 hr in a UDS level comparable with that in chick fibroblast-normal human heterokaryons. In heterokaryons obtained after fusion of chick fibroblasts with XP group C cells UDS remains at the level of chick cells. These data suggest that reactivation of chick erythrocyte nuclei results in expression of repair functions which are able to complement the defects in the XP complementation groups A, B, C and D. (Author abstract) (15 Refs)

37. CYTOGENETIC ANOMALIES IN A PATIENT WITH ATAXIA, IMMUNE DEFICIENCY, AND HIGH ALPHA-FETOPROTEIN IN THE ABSENCE OF TELANGIECTASIA.

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Childrens Hosp. Los Angeles, 4650 Sunset Blvd., P.O. Box 54700, Los Angeles, CA, 90054
Cancer Genet Cytogenet; 4(4):311-317 1981

A 58-yr-old male with spinocerebellar degeneration in association with choreiform movement is described. He possessed neurological, biochemical, immunological, as well as cytogenetic disorders predisposing to cancer similar to patients with ataxia telangiectasia (AT). Cytogenetic abnormalities included four abnormal clones: trisomy 14;t(13;14);t(7,14)(q32;q12); and t(7;14)(p13;q12), in addition to breaks, rings, and acentric chromosomes. The absence of telangiectasia, the late onset of neurological symptoms, and the prolonged survival in this case may separate it from the classic AT. Although the syndrome may be recognized as a new chromosome instability syndrome, multiple allelism may play a role in the expression of a milder form of AT. (Author abstract) (19 Refs)

38. GENETICS IN GESTATIONAL TROPHOBLASTIC DISEASE.

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Excerpta Med Int Congr Ser; 551:409-412 1981

The pathogenetics of gestational trophoblastic disease are discussed. Choriocarcinoma can follow the birth of a normal male or female child Invasive mole or choriocarcinoma can follow a pregnancy with a hydatidiform mole. Cytogenetic and biochemical marker studies show complete moles have no genetic contribution from the female parent, are diploid and, except in rare cases, have a female sex chromosome constitution and are homozygous for the genetic contribution of the male parent. In typical cases, complete mole was heterozygous for phosphoglucomutase 1, acid phosphatase, glyoxalase, esterase D, and phosphoglycolate phosphatase (PGP). Maternal exclusion was shown at the PGP locus patient type 1, husband 2-1 and male 2. All partial moles studied were triploid. In all such cases, findings were compatible with fertilization of a haploid egg by two sperms. Partial moles, in contrast to complete moles, are often heterozygous, a maternal contribution was identified, and the trisomic state was sometimes identified by enzyme pattern. Spontaneously aborted triploids, like partial moles, show a deficiency of the XYY chromosome complement; the XXY to XXX ratio favors a preponderance of origin by diandry in both triploid abortuses and partial moles. Although all cases of hydatidiform moles studied that required chemotherapy were complete moles, partial moles may also require such therapy. (15 Refs)

39. GESTATIONAL TROPHOBLASTIC DISEASE: MORPHOLOGY AND PATHOGENESIS.

Brewer JI, Mazur MT
Dept. Obstetrics and Gynecology, Northwestern Univ. Medical Sch., Chicago, IL
Excerpta Med Int Congr Ser; 551:398-404 1981

Morphological aspects in the development of choriocarcinoma and hydatidiform mole are discussed. Pregnancies in six patients with choriocarcinoma progressed normally until the onset of symptoms at 17, 24, 26, 32, 35, and 1 wk after term delivery at 40 wk. Initial symptoms were produced by metastatic lesions vagina (3), brain (2), lungs (1). Microscopically in 5/5 placentas that appeared normal grossly, small primary choriocarcinoma lesions were found by extensive examination. Observations of these patients revealed that choriocarcinoma can arise from the chorionic villi at any time during a seemingly normal pregnancy, that it can be present for some time without producing symptoms referable to the uterus or the pregnancy, and that in its earlier stages of development it is associated with villi. Cytogenetic studies of hydatidiform mole have revealed chromosomal anomalies in some and normal karyotypes in others. Partial mole by morphologic criteria does not give rise to invasive mole and choriocarcinoma. Observations reported indicate that, from a morphologic standpoint, hydatidiform mole is a single entity. (6 Refs)

40. HYDATIDIFORM MOLE IN THE UNITED STATES (1970-1977): A STATISTICAL AND THEORETICAL ANALYSIS.

Hayashi K, Bracken MB, Freeman DH, Hellenbrand K
(c/o Bracken) Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, 60 College St., New Haven, CT, 06510
Am J Epidemiol; 115(1):67-77 1982

The incidence of hydatidiform mole and some epidemiologic features of the disease in the United States were studied. Data for the present study were obtained from the Hospital Discharge Survey (1970-1977) of the National Center for Health Statistics. The estimated incidence of hydatidiform mole over the 8-yr period was 108.4 per 100,000 pregnancies (SE = 10.3) or 1 case in every 923 pregnancies. There was an apparent increase in the incidence rate from 1970 to 1975, but the rate dropped slightly after 1975. The distribution of hydatidiform mole by maternal age showed the highest rate among women 35 yr and older, and the second highest rate among women aged 15-19. The distribution by maternal age found for the entire sample was also apparent within each race category. Overall, black women appeared to have an incidence rate half that of white women. Regional differences in the United States were observed in spite of race and age adjustment. Existing studies are reviewed in light of morphologic and cytogenetic classification schemes and a recent hypothesis for the androgenetic origin of hydatidiform mole. A fresh approach to the epidemiology of hydatidiform mole which combines epidemiologic and genetic studies is indicated. (Author abstract) (44 Refs)

CHROMOSOMES OF HUMAN CELL LINES AND TUMORS IN VITRO

41. ESTABLISHMENT OF CELL LINES DERIVED FROM SQUAMOUS CELL CARCINOMA OF THE ESOPHAGU S IN HUMANS AND RATS.

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Jpn J Clin Oncol; 11(3):487-493 1981

Two esophageal carcinoma cell lines (TH and TS) were established in DM-160 medium containing 20% fetal bovine serum, and their cytology, chromosomes, and electrophoretic lactate dehydrogenase (LDH) isozyme patterns were studied. Three cell lines (R-1, R-2, R-3) from Donryu rats whose esophageal tumors had been induced by N-amyl-N-methyl-nitrosamine were also established, and subjected to the same studies. The modal chromosome numbers were as follows: TH, 46; TS, 59; R-1, 68; R-2, 41; R-3, 73. The LDH isozyme pattern studied in the TH cell line indicated a tumor pattern. Human tumor cells were sc transplanted to BALB/C nude mice; rat cell lines were transplanted to both mice and Donryu rats. All cell transplants to nude mice resulted in tumors, but transplants in syngeneic Donryu rats did not develop into tumors. (8 Refs)

42. THE RIDDLE OF HODGKIN CELLS.

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MMW; 123(48):1827-1828 1981

Characteristics of the first tumor cell cultures successfully established from biopsy material of patients with Hodgkin's disease are described. Testing for markers of differentiation revealed that the cell lines had antigenic properties similar to those of early myelo-monocytes. Although the cell lines were established from biopsy specimens of four patients, they possessed many identical characteristics, identical marker chromosomes, and common cytochemical features. One of the four cell lines was positive for an Epstein-Barr-virus (EBV)-induced antigen, and another cell line possessed EBV receptors. The cell lines were poor inducers of tumor growth in nude mice. (no Refs) (In GER)

43. HUMAN ERYTHROID CELL LINES DERIVED FROM A PATIENT WITH ACUTE ERYTHREMIA.

Okano H, Okamura J, Yagawa K, Tasaka H, Motomura S
Dept. Pathology, Kyushu Cancer Center Res. Inst., 595 Notame, Minami-ku, Fukuoka 815, Japan
J Cancer Res Clin Oncol; 102(1):49-55 1981

Three continuous human cell lines, designated KMOE, derived from a patient with acute erythremia (Di Guglielmo's disease) are reported. The cell lines are the cultures of (1) bone marrow cells, (2) peripheral blood cells, and (3) cells from a tumor developed into an athymic nude mouse after transplantation of the cultured bone marrow cells. Cells of all three lines show morphology of immature erythroblast and have i(17q) marker chromosome. They are negative for both Philadelphia chromosome and Epstein-Barr virus nuclear antigen. Although all KMOE cells in suspension culture are benzidine-negative, benzidine-positive cells are found within colonies formed in semi-solid culture media. The relative number of colonies with benzidine-positive cells is increased when sodium butyrate is added to the culture. The KMOE cell lines are human erythroid cell lines with erythroblastic morphology and still retain their tendency for differentiation. (Author abstract) (9 Refs)

44. A T-CELL LINE DERIVED FROM NORMAL HUMAN CORD LEUKOCYTES BY CO-CULTURING WITH HUMAN LEUKEMIC T-CELLS.

Miyoshi I, Kubonishi I, Yoshimoto S, Shiraishi Y
Dept. Medicine, Kochi Medical Sch., Oko-cho, Nankoku-shi, Kochi-ken 781-51, Japan
Gan; 72(6):978-981 1981

A unique T-cell line, MT-2, was established from normal human cord leukocytes of a male infant by co-culturing with leukemic T-cells from a female patient with adult T-cell leukemia. MT-2 cells expressed receptors for sheep erythrocytes and complement and were reactive with anti-T-cell and anti-Ia sera. They were negative for Fc receptors, surface immunoglobulin, and Epstein-Barr virus nuclear antigen. Chromosomally, the MT-2 line was male and most cells were shown to have a normal diploid karyotype. The cultured cells were tumorigenic when transplanted into immunosuppressed newborn hamsters. (Author abstract) (11 Refs)

45. TRANSFORMATION OF NORMAL HUMAN CORD LYMPHOCYTES BY CO-CULTIVATION WITH A LETHALLY IRRADIATED HUMAN T-CELL LINE CARRYING TYPE C VIRUS PARTICLES.

Miyoshi I, Yoshimoto S, Taguchi H, Ohtsuki Y, Kubonishi I, Shiraishi Y, Akagi T
Dept. Anataomy, Kochi Medical Sch., Oko-cho, Nankoku-shi, Kochi-ken 781-51, Japan
Gan; 72(6):997-998 1981

Normal human cord WBC were co-cultured with lethally irradiated MT-2 cells to produce a T-cell line of cord WBC origin which harbored type C virus particles and adult T-cell leukemia-associated antigens (ATLA). On the 11th day of culture, 1 x 10(6) lethally x-irradiated (6,000 R) MT-2 cells were added to two of four dishes of cord WBC. Control cultures included two dishes of irradiated MT-2 cells without cord WBC and two dishes of cord WBC alone. All cultures were incubated at 37 C in a humidified 7.5% CO2 atmosphere. Two wk after co-culture, scattered foci of cell aggregates were observed on the sheets of macrophages. Continuous growth of cells developed in two of the co-cultured dishes, and this cell line, designated Ok, was maintained in culture for 3 mo. The Ok line consisted of mostly immature lymphoid cells with multinucleate giant cells. Sixty-six percent of the Ok cells formed spontaneous rosettes with neuraminidase-treated sheep RBC. Most of the Ok cells were positive for Leu-1 and OK11, but negative for Leu-2a and Leu-3a. None of the 145 Ok cells studied contained a Y chromosome; 41/46 cells had a 46,XX karyotype. Electron microscopy revealed many type C virus particles in the extracellular spaces. Most of the Ok cells were positive for ATLA when reacted with ATL patient's sera. The cultured cells gave a positive reaction with five sera from ATL patients but not with five sera from normal control individuals. These findings suggest that the type C virus was apparently transmitted from the MT-2 cells to the cord lymphocytes during co-cultivation. (8 Refs)

46. ESTABLISHMENT AND CHARACTERIZATION OF A CELL LINE (SS78) FROM A HUMAN RENAL CELL CARCINOMA.

Shrivastav S, Sharief Y, Day J, Reich CF, Bonar RA
Duke Univ. Medical Center, Box 3813, Durham, NC, 27710
In Vitro; 17(12):1117-1124 1981

A new cell line, SS78, was established from a primary renal cell carcinoma of a Caucasian male. The tissue was dispersed with collagenase, and viable cells were separated by flotation on a Ficoll-Hypaque gradient. In culture, the SS78 cells retained a distinct epithelial morphology, and no fibroblastlike cells were seen. The cultured cells were aneuploid with a modal chromosome number of 80 and had several marker chromosomes. Inoculation of the cultured cells into athymic nude mice caused tumors at the sites of inoculation. (Author abstract) (32 Refs)

47. SPECIFIC CHROMOSOME LOSS ASSOCIATED WITH THE EXPRESSION OF TUMORIGENICITY IN HUMAN CELL HYBRIDS.

Stanbridge EJ, Flandermeyer RR, Daniels DW, Nelson-Rees WA
Dept. Microbiology, Coll. Medicine, Univ. California, Irvine, Irvine, CA, 92717
Somatic Cell Genet; 7(6):699-712 1981

Four related nontumorigenic and tumorigenic HeLa x fibroblast intraspecific human hybrid cell lines were analyzed to determine whether specific chromosomes are associated with the control of tumorigenic expression. All four cell lines examined (CGL1, CGL2 nontumorigenic; CGL3, CGL4 tumorigenic) were derived from a single fusion between the HeLa variant D98/AH-2 and a normal male fibroblast cell strain GM77. The purity of cell population was readily evaluated because of the morphologic differences between the nontumorigenic cell lines and their tumorigenic counterparts. Characteristic HeLa marker chromosomes were seen in all metaphases of D98/AH-2 cells and the four hybrid cell cultures. The complexity of different HeLa marker chromosomes compared within and between hybrid clones did not permit a definition of tumorigenic vs nontumorigenic based on the presence or absence of known HeLa markers. The two tumorigenic cell lines, CGL3 and CGL4, contained three copies/metaphase of both chromosomes 11 and 14. The nontumorigenic CGL1 and CGL2 cell lines contained four copies/metaphase of chromosome 11 and 14. This difference is highly significant according to statistical analysis. The tumorigenic segregants were derived from the original nontumorigenic hybrid population. The parental origin of the chromosomes could not be established. Preliminary results suggest that complex regulatory interactions may operate in the control of neoplastic expression. (43 Refs)

CHROMOSOMES OF ANIMAL CELL LINES AND TUMORS

48. ISOLATION AND PARTIAL CHARACTERIZATION OF MUTAGEN-SENSITIVE AND DNA REPAIR MUTANTS OF CHINESE HAMSTER FIBROBLASTS.

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Environ Mutagen; 3(1):53-64 1981

Isolation and partial characterization of several mutants of Chinese hamster cells, which are affected in their ability to repair DNA damage or in their sensitivity to radiation or chemical mutations, are discussed. Cells of a subclone of the V79 aneuploid cell line were mutagenized by combined treatment with 5-bromodeoxyuridine and blacklight, followed by UV irradiation. 3H-thymidine was incorporated in repair-proficient cells at high temperature (38.5 C) following UV damage. Cells were held in the cold (4.0 C) to induce radioactive thymidine killing. Repair-deficient and UV-sensitive cells which had survived and formed colonies at low temperature (34.0 C) were tested for recovery. Seventy-two surviving colonies were isolated from 2 x 10(7) cells plated for selection. Four colonies were selected for extensive study. Colony UVs-7 was slightly more sensitive to UV, but not sensitive to x-rays or N-acetoxy-2-acetylaminofluorene (NAc-AAF); this mutant exhibited a highly reduced level of unscheduled DNA synthesis (UDS), as compare to the parental line. UVs-40 and UVs-44 line colonies were sensitive to UV, x-ray, N-methyl-N-nitro-N-nitrosoguanidine, and NAc-AAF, but exhibited normal UDS. Line UVr-23 had enhanced UDS, was resistant to UV, but exhibited no difference in sensitivity to x-ray or NAc-AAF. These four mutants are all stable, and may be useful for the study of mammalian DNA repair processes and mechanisms of mutagenesis. (38 Refs)

49. DECREASED TUMORIGENICITY OF RODENT CELLS AFTER FUSION WITH LEUKOCYTES FROM NORMAL AND LEUKEMIC DONORS.

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Dept. Cell Biology and Genetics, Erasmus Univ., Rotterdam, The Netherlands

Somatic Cell Genet; 7(6):645-656 1981

Hybrid cell lines, derived from fusion of tumorigenic rodent cells (mouse Pg 19 or Chinese hamster a3) with WBC from leukemic donors were isolated and tested for growth in congenitally athymic nude mice. Cytogenetic analysis, using banding techniques, was performed on cells before injection and on the tumors which eventually developed. Pg 19 mouse cells alone were highly tumorigenic; 1 x 10(5) cells resulted in 100% tumors. The a3 grew more slowly and 2 x 10(6) cells were needed to produce tumors in 75% of mice in 10 days. WBC from chronic myeloid leukemia donors, with inocula of up to 4 x 10(7) cells, failed to form tumors within 3 mo in nude mice, further immunosuppressed by ip cyclophosphamide. The chromosome analyses did not reveal a human chromosome-bearing factor(s) which singly appeared responsible for the tum or suppression. The presence of the Philadelphia translocation in the leukemic cells does not appear to have deprived these cells of their tumor-suppressing ability. (29 Refs)

50. ALTERED PROPERTIES OF TUMORS INDUCED BY ADENOVIRUS TYPE 12 DNA FRAGMENT TRANSFORMED CELLS AFTER GROWTH IN IMMUNOCOMPETENT RATS.

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Int J Cancer; 29(1):101-105 1982

The GY1-3-1 cell line, which was derived from a rat cell line transformed by the Ad 12 HindIII-G fragment, can induce tumors in newborn rats, but not in mature rats. However, when 10 mature rats were transplanted with a large number of GY1-3-1 tumor fragments, two developed tumors with a long latency period. These two tumors (GY1-3M and GY1-3Y) were quite different in properties from the originally inoculated GY1-3-1 tumor. Tumor transplantation studies revealed that both GY1-3M and GY1-3Y tumors could grow in mature rats, and the number of takes with transplanted tumor was 100% with GY1-3M tumor and 40% with GY1-3Y tumor. Histopathologically original GY1-3-1 tumor showed a morphology of undifferentiated sarcoma, while the histologic picture of GY1-3M and GY1-3Y tumors was similar to that encountered in human fibrosarcoma and malignant fibrous histiocytoma, respectively. Both GY1-3M and GY1-3-1 tumors, when recultured in vitro, gave rise to cell lines with a fibroblastic appearance, although the original GY1-3-1 cell line exhibited an epithelioid morphology. In chromosome analysis, the GY1-3-1 cell line was pseudodiploid, while the cell lines from GY1-3M and GY1-3Y tumors were hyperdiploid or near-triploid. The metacentric marker chromosome, M1, was present in mitotic cells of the GY1-3-1 line and of the GY1-3M tumor lines, but absent from the GY1-3Y tumor lines. By Southern blot hybridization, multiple bands of cellular DNAs from parental GY1-3-1 cells hybridized with labeled Ad12 HindIII-G, while only a single band hybridized in DNAs from both GY1-3M and GY1-3Y tumors. (Author abstract) (15 Refs)

51. CYTOGENETICS OF MURINE THYMIC LYMPHOMAS INDUCED BY N-METHYL-N-NITROSOUREA: DIFFERENCE IN INCIDENCE OF TRISOMY 15 IN THYMIC LYMPHOMAS INDUCED IN NEONATAL AND ADULT MICE.

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Dept. Anatomy, Health Sciences Center, Univ. Western Ontario, London, Ontario N6A 5C1, Canada
Cancer Genet Cytogenet; 4(4):337-344 1981

Chromosome complements of murine thymic lymphomas induced by an alkylating agent N-methyl-N-nitrosourea (MNUA) were analyzed microscopically and karyotypically using the Q-banding technique. The chemical carcinogen was injected intraperitoneally into either neonatal or 7-wk-old CFW/D mice. In addition, thymic lymphomas induced in 7-wk-old AKR mice and thymic lymphomas developed spontaneou sly in this strain were also examined. All six lymphomas induced in neonatal CFW/D had hyperdiploid cell lines that accounted for 90% of the cells analyzed. Chromosome analysis of lymphomas induced in adult CFW/D mice showed that only four out of nine lymphomas had predominantly hyperdiploid cell lines. The remaining five lymphomas had diploid modal chromosome number although they also carried a variant line characterized by 41 chromosomes. All eight lymphomas induced in adult AKR mice and six out of seven spontaneous AKR lymphomas showed predominantly diploid modal line. The remaining spontaneous lymphoma had a hyperdiploid stem line of 41 chromosomes. Microscopic and karyotypic analysis further identified trisomy 15 as the regular chromosome abnormality in the hyperdiploid cells in lymphomas of each group, whereas cells with diploid chromosome number had no detectable chromosome abnormality. Additional trisomies were also found, but their appearance was restricted to individual tumors. Thus, the incidence of trisomy 15 in lymphomas induced by MNUA in adult CFW/D and AKR mice, as well as in the spontaneous AKR lymphomas, is significantly lower than that in lymphomas induced in neonatal mice by the same carcinogen. (Author abstract) (19 Refs)

52. CLONAL ANALYSIS OF H-2 ANTIGEN EXPRESSION BY VARIANTS OF A CHEMICALLY INDUCED MURINE TUMOR.

Schirrmacher V, Robinson P, Altevogt P, Radbruch A, Garrido F, Koszinowski U, Krog HH, Lundin L, Martin MJ, Parmiani G, Alexander P
Institut fur Immunologie und Genetik, DKFZ, Heidelberg, W. Germany
Transplant Proc; 13(4):1819-1823 1981

Expression of foreign H-2 antigens by cell lines derived from a methylcholanthrene-induced BALB/c mouse tumor (MCG4) was studied using cloned cell lines. Analysis of 65 clones showed heterogeneity of morphology and H-2 phenotype, represented by three main cell forms. Large, pseudotetraploid cells (70 chromosomes) without H-2 antigen were exemplified by clone 31. Small, pseudodiploid cells (38 chromosomes) with H-2d-like phenotype were exemplified by clone 38. Small, pseudodiploid cells (38 chromosomes) with H-2k-like phenotype were exemplified by clone 52. A number of clones expressing H-2b phenotype and C57BL/6 genetic markers were excluded from the study because BALB/c origin of the cells could not be confirmed. Analysis of five isoenzymes showed that tumor cells bearing foreign H-2k determinants shared ES-3, Id-1, ES-1, and Gus isoenzymes with BALB/c cells, but differed in the GpI isoenzyme. Immunochemical analysis of 35S-labeled cells showed that rabbit anti-H-2 serum precipitated H-2d-like molecules from clone 38, H-2k-like molecules from clone 52, and nothing from clone 31. Results of inoculation of BALB/c and (BALB/c x B10.BR)F1 mice with cells from clones 52 and 38 showed that mice capable of responding to H-2k antigens re sisted tumor cells expressing H-2k-like antigen, but they did not show resistance to cells expressing the H-2d-like antigen. (9 Refs)

53. ELECTROPHORETIC MOBILITY OF MOUSE T-CELL HYBRIDS.

Bubenik J, Perlmann P, Jonsdottir I, Kypenova H, Bubenikova D, Simova J
Inst. Molecular Genetics, Czechoslovak Academy Sciences, 160 00 Prague 6, Czechoslovakia
Br J Cancer; 44(5):692-699 1981

The hybrid cell line BH2 was derived by fusion between an AKR thymoma BW5147 (HGPRT(-)) and C57BL thymoma EL-4R (TK(-)). The hybrid cells showed a near-tetraploid modal number of chromosomes, in contrast to the near-diploid stem-lines of both parental cell populations; most of the BH2 hybrid cells acquired marker chromosomes from both parenteral cell lines. Inoculation of the parental and hybrid cells into C57BL and AKR mice revealed that the possible admixture of revertant parental cells in the hybrid cell population was less than 10(-4). Anodic electrophoretic mobilities (AEM) of the mouse thymoma lines and their hybrids were compared with each other and with normal mouse lymphoid cells. The AEM of the parental and hybrid T-cell lines was slower than that of mouse T LNC and comparable with AEM of some thymocyte subsets. The mean AEM of parental and hybrid cell lines was 0.69 um/sec/V/cm for BW5147 cells, 0.96 for EL-4R cells and 0.83 for BH2 cells, the mean AEM of the hybrid cell population being identical with the mean of the parental AEM values. The mean AEM was found to be a relatively stable characteristic of each cell line. (Author abstract) (33 Refs)

54. CHARACTERIZATION OF A BONE MARROW CELL LINE TRANSFORMED BY ABELSON'S MURINE LEUKEMIA VIRUS.

Pinter A, Borzsonyi M
Orszagos Kozegeszsegugyi Intezet, Budapest, Hungary
Magy Onkol; 25(4):217-226 1981

Development of transformed cell line (Gr 17) was observed after infection of a long-term bone marrow cell culture from BALB/c mice with Abelson's murine leukemia virus (strain P 160) (A-MuLV). According to their phenotype, the Gr 17 cells corresponded to the early maturation form of B lymphoid cells (pre-B lymphoblasts). The results of the tests for alpha-naphthylacetate esterase, Hb, phagocytosis, and membrane surface Ig were negative, but cytoplasmic IgM was found. In contrast to the hitherto described cell lines obtained by transformation with A-MuLV, hypodiploid chromosome set and the presence of metacentric chromosome due to translocation were observed. Development of thymus-independent generalized lymphoma was observed after transplantation of Gr 17 cells (2 x 10(7) cells iv) in 4-6-wk-old male and female BALB/c mice. The take rates were 9/10 in the females and 8/10 in the males. The mean latent periods were 41 days in the females and 50 days in the males. Typical Abelson's tumors were induced by the virus produced by the cell line in newborn BALB/c mice. (27 Refs) (In HUN)

55. ESTABLISHMENT OF B-LYMPHOBLASTOID CELL LINES FROM MAREK'S DISEASE VIRUS-INDUCED TUMORS IN TURKEYS.

Nazerian K, Elmubarak A, Sharma JM
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Int J Cancer; 29(1):63-68 1982

Four lymphoblastoid cell lines were established from tumors of turkeys inoculated with high doses of the GA strain of Marek's disease virus (MDV). Unlike other MD lymphoblastoid cell lines of chicken origin, these MDV transformed turkey lines appear to be B lymphocytes and produce immunoglobulin. Growth characteristics of these cell lines are slightly different; however, they all produce low levels of MDV-specific antigen and carry the complete genome of the virus as determined by virus rescue in the chicken or in duck embryo fibroblast cultures. These cell lines are pathogenic for chickens and produce virus-induced MD lesions. All four lines are free of the herpesvirus of turkeys, reticuloendotheliosis virus, and three lines are also free of avian leukosis virus. They all have typical normal turkey chromosomes and are positive for Marek's disease tumor-associated surface antigen. (Author abstract) (24 Refs)

56. AGING AND SISTER CHROMATID EXCHANGE. VIII. EFFECT OF THE AGING ENVIRONMENT ON SISTER CHROMATID EXCHANGE INDUCTION AND CELL CYCLE KINETICS IN EHRLICH ASCITES TUMOR CELLS. A BRIEF NOTE.

Schneider EL, Lewis J
Biomedical Res. and Clinical Medicine Program, Natl. Inst. on Aging, NIH, Bethesda, MD, 20205
Mech Ageing Dev; 17(4):327-330 1981

To examine the effect of an aging environment on sister chromatid exchange (SCE) induction, Ehrlich ascites tumor (EAT) cells were introduced into young and old C57BL/6J mice. Background SCE levels were not significantly different in either EAT cell or normal bone marrow cell populations between young and old animals. Despite a decline in SCE induction in bone marrow cells in older mice at high mitomycin C concentrations, SCE induction in EAT cells was not significantly affected by the age of the animal. These findings suggest that the aging environment may not play a major role in the diminished SCE induction observed in old cell populations. (Author abstract) (8 Refs)

57. GENETIC CONTROL OF ROUS SARCOMA REGRESSION IN INBRED LINES OF CHICKENS.

Plachy J, Albrecht V
Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 160 00 Praha, Czechoslovakia
Folia Biol (Praha); 27(5):289-300 1981

The fate of tumors induced by the Prague strain of Rous sarcoma virus (RSV) subgroup C was studied in highly inbred chicken lines. The lines CB and CC, and WA and WB, congeneic at the B complex, the major histocompatibility complex of the chicken, were used. The CB and CC lines differ only in the B haplotype, as do the WA and WB lines. Included in the study were (CB x CC)F1 hybrids and backcross progeny of the CB and CC lines. All birds were blood typed before use. Birds received 10(3), 10(2), or 10(1) focus-forming units/animal sc in the left wing web. The pattern of tumor regression or progression was assessed weekly beginning 7 days post-inoculation for a 10 wk period, in birds 4-8 wk, 12-16 wk, or 1 yr old at the time of inoculation. Results demonstrated that Rous sarcoma regression in the congeneic CB and CC lines is controlled by a gene within the B region of the chromosome. Another congeneic pair in the WA and WB lines also differed in ability to regress RSV-induced tumors and a gene within the B complex also appeared to have a significant role in the regression of Rous sarcoma. (24 Refs)

GENE MAPPING STUDIES

58. CELL ONCOGENES ARE LOCATED ON THE LARGE MICROCHROMOSOMES IN CHICKEN CELLS.

Tereba A, Lai MM
Div. Virology, St. Jude Children's Res. Hosp., Memphis, TN, 38101
Virology; 116(2):654-657 1982

The chromosomal locations of c-myc and c-myb, the cell homologs of the transforming genes present in myelocytomatosis virus 29, MC29, and avian myeloblastosis virus, AMV, respectively, were determined in White Leghorn chickens using in situ hybridization. Nucleic acid probes containing MC29 and AMV-RNAs were used to localize both c-myc and c-myb to a subset of large microchromosomes. The chromosomal location of c-myc was confirmed using nucleic acid probes containing RNA from MH-2, which also contains a myc-like sequence, and cloned DNA containing the chicken c-myc gene. In conjunction with our previous results localizing c-src and c-erb, we have demonstrated that several cell oncogene homologs appear to be localized on a subset of large microchromosomes. (Author abstract) (18 Refs)

59. THE ONCOGENICITY OF AVIAN ADENOVIRUSES. III. IN SITU DNA HYBRIDIZATION OF TUMOR LINE CELLS LOCALIZED A LARGE NUMBER OF A VIROCELLULAR SEQUENCE IN FEW CHROMOSOMES.

Yasue H, Ishibashi M
(c/o Ishibashi) Lab. Viral Oncology, Aichi Cancer Center, Res. Inst., Nagoya, Aichi, 464, Japan
Virology; 116(1):99-115 1982

The arrangement of the viral DNA in a CELO virus (an avian adenovirus)-induced rat tumor cell line was analyzed at the molecular and the cellular level. Blot hybridization of restriction endonuclease-digested tumor cell DNA and quantitative hybridization of nondigested tumor cell DNA with 32P-labeled restriction endonuclease-generated fragments of the viral DNA indicate the following: (1) A contiguous portion of the viral DNA comprising 33% of the viral DNA molecules [ie, 14.1 kilobases (kb)] is flanked at each terminus by a cellular DNA sequence. This viral DNA sequence, together with greater than 6.1 kb of one of the flanking cellular DNA sequences and greater than 6.8 kb of the other, forms repetition unit (total length greater than 27 kb). (2) During the evolution of the original tumor, this unit has attained as many as 160 copies per diploid amount of cellular DNA. In situ DNA hybridization of the cultured tumor cells with 3H-labeled viral DNA indicates that most of the repetition units are constituents of chromosomal DNA and their distribution is limited to only a few chromosomes per hypotetraploid tumor cell. The majority of chromosomes carrying a large number of repetition units are abnormal chromosomes longer than rat chromosome No 1. (Author abstract) (16 Refs)

60. INTEGRATION SITE OF POLYOMA VIRUS DNA IN THE INDUCIBLE LPT LINE OF POLYOMA-TRANSFORMED RAT CELLS.

Mendelsohn E, Baran N, Neer A, Manor H
Dept. Biology, Technion-Israel Inst. Technology, Haifa, Israel
J Virol; 41(1):192-209 1982

The structure of polyoma virus (Py) integration site in the inducible LPT line of Py-transformed rat cells was determined by biochemical methods of gene mapping. The data indicate that LPT cultures contain Py insertions of various lengths integrated into the same chromosomal site in all the cells. The length heterogeneity of the viral insertions is due to the presence of 0, 1, 2, 3... Py genomes arranged in a direct tandem repeat within invariable sequences of viral DNA. Double-digestion experiments were also carried out with the above enzymes and with enzymes that cleave the Py genome at multiple sites. The data obtained in these experiments were used to construct a physical map of the integration site. This map showed that the early region of the virus remained intact even in the smallest insertion (which contains no whole duplicated genomes), whereas the late region was partially duplicated and split during integration. The smallest insertion is colinear with the Py physical map over a region including the entire Py genome and at least a part of the duplicated segment. This structure could give rise to nondefective circular viral DNA molecules by single homologous recombination events. Similar recombination events may occur at a higher frequency in the longer insertions, which include longer regions of homology, and may yield many more free viral genomes. The presence of these insertions in LPT cells could thus by one of the factors which account for the high inducibility of the LPT line. (34 Refs)

61. GENETICS OF THE ALPHA 1,6-DEXTRAN RESPONSE: EXPRESSION OF THE QUPC52 IDIOTYPE IN DIFFERENT INBRED AND CONGENIC STRAINS OF MICE.

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Litton Bionetics, Kensington, MD, 20795
J Immunol; 128(1):492-497 1982

Antibodies to dextran B512 were raised in various strains of mice and were assayed by a radioimmunoassay procedure. Idiotypic antibodies to the IgA(k) dextran B512 binding myeloma proteins QUPC52 and W3129 of BALB/c origin were prepared in rabbits. After adsorption, each antiserum was specific for the immunizing myeloma protein and did not react with hundreds of other myeloma proteins; nonetheless, antibodies to dextran B512 from various strains of mice cross-reacted in these test systems. Of the two idiotypes tested, the W3129 idiotype was more universally expressed in different strains of mice. The QUPC52 idiotype was the predominant idiotype in BALB/c anti-dextran B512 antibodies and was found in only a few other inbred strains. Using a battery of congenic and inbred strains, it was shown that the QUPC52 idiotype was controlled by genes linked to the Igh complex locus (chromosome 12) and to the Ig kappa complex locus (chromosome 6). The W3129 idiotype was found in a number of stocks of mice in the genus Mus recently isolated from the wild. The QUPC52 idiotype thus far was found only in inbred mice. (Author abstract) (26 Refs)

MOLECULAR CYTOGENETICS

62. LOSS AND STABILIZATION OF AMPLIFIED DIHYDROFOLATE REDUCTASE GENES IN MOUSE SARCOMA S-180 CELL LINES.

Kaufman RJ, Brown PC, Schimke RT
(c/o Schimke) Dept. Biological Sciences, Stanford Univ., Stanford, CA, 94305
Mol Cell Biol; 1(12):1084-1093 1981

Loss and stabilization of dihydrofolate reductase (DHFR) genes in clones of methotrexate (MTX)-resistant mouse S-180 cells were determined using the fluorescence-activated cell sorting technique. Multiple copies of the DHFR gene in the cells were associated with double minute (DM) chromosomes. In the absence of MTX, the growth rate of cells was inversely related to the degree of gene amplification (number of DM chromosomes). Unequal distribution of DM chromosomes into daughter cells at mitosis could result in gain or loss of genes. Loss of amplified DHFR genes during growth in the absence of MTX was related to the continual generation of cells with lower numbers of DM chromosomes. This growth advantage led to dominance of the cells in the population. An unstably resistant S-180 cell line clone generated cells with stably amplified DHFR genes after 3 yr of continuous growth; the DHFR genes were present on one or more chromosomes and were retained in a stable state. (28 Refs)

63. RELATIONSHIP OF AMPLIFIED DIHYDROFOLATE REDUCTASE GENES TO DOUBLE MINUTE CHROMOSOMES IN UNSTABLY RESISTANT MOUSE FIBROBLAST CELL LINES.

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Mol Cell Biol; 1(12):1077-1083 1981

The localization of unstably amplified dihydrofolate reductase (DHFR) genes to double minute (DM) chromosomes was determined in the methotrexate (MTX) resistant 3T6 and 3T3 mouse cell lines. Cells were labeled with a fluoresceinated derivative of MTX and analyzed by a fluorescence-activated cell sorting technique. 3T6 cells selected in increasing concentrations of MTX were unstable for DHFR overproducti on and MTX resistance when cultured in the absence of MTX. Karyotypic analyses of both cell lines revealed DM chromosomes not present in the parental cell strains. Essentially identical kinetics of DHFR gene sequence loss of total DNA and of DNA from fractions enriched in DM chromosomes were observed during reversion to MTX sensitivity; the finding suggested localization of unstably amplified gene sequences on DM chromosomes. Analysis of cell populations sorted according to DHFR content showed a proportional relationship between gene amplification and enzyme content in the DM chromosome. (27 Refs)

64. GENE AMPLIFICATION IN METHOTREXATE-RESISTANT MOUSE CELLS. III. INTERRELATIONSHIPS BETWEEN CHROMOSOME CHANGES AND DNA SEQUENCE AMPLIFICATION OR LOSS.

Tyler-Smith C, Bostock CJ
Medical Res. Council Mammalian Genome Unit, King's Building, West Mains Road, Edinburgh EH9 3JT, Scotland
J Mol Biol; 153(2):237-256 1981

The amplified DNA sequences within a single subline of methotrexate-resistant mouse cells have a complex intracellular location, some being associated with 'double minute' chromosomes, and some with normal-sized chromosomes. However, within a cell line and probably within a cell their internal structure is stable and homogeneous. These results, and those from the previous paper, suggest that gene amplification in these cells has two distinct stages. Firstly, an amplifiable unit is generated by a process involving DNA rearrangement. Secondly, the unit increases in number but remains unchanged in structure. (Author abstract) (17 Refs)

65. GENE AMPLIFICATION IN METHOTREXATE-RESISTANT MOUSE CELLS. II. REARRANGEMENT AND AMPLIFICATION OF NON-DIHYDROFOLATE REDUCTASE GENE SEQUENCES ACCOMPANY CHROMOSOMAL CHANGES.

Bostock CJ, Tyler-Smith C
Medical Res. Council Mammalian Genome Unit, King's Building, West Mains Road, Edinburgh EH9 3JT, Scotland
J Mol Biol; 153(2):219-236 1981

Total amplified DNA in methotrexate-resistant mouse lymphoma EL4 cells and mouse melanoma PG19 cells has been characterized in two ways. Metaphase spreads show the presence of additional chromosome forms that are either 'homogeneously staining' chromosomes or 'double minute' and ring chromosomes. Gel electrophoresis of restriction enzyme-digested nuclear DNA shows the presence of amplified sequences, the pattern of which is unique in each of five cell lines. We conclude that extensive DNA rearrangement has taken place during amplification. (Author abstract) (38 Refs)

66. MELPHALAN PREVENTS THE FORMATION OF DOUBLE-STRANDED DNA REPLICATION INTERMEDIATES IN HUMAN MALIGNANT MELANOMA CELLS.

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Carcinogenesis; 2(12):1311-1316 1981

When human melanoma cells are lysed in a neutral buffer they release from the chromosomes double-stranded DNA replication intermediates. We have now examined the effect of a bifunctional alkylator (melphalan) on the formation of these intermediates. After treatment for 25 min there is little or no release of double-stranded DNA intermediates from the chromosomes. When the cells are washed free of the drug and cultivated further there is a resumed formation of the DNA intermediates. This is paralleled by the finding that the cells, when the drug is removed, after a time-lag, regain the capacity to proliferate. (Author abstract) (7 Refs)

67. SEPARATION OF BASAL HISTONE SYNTHESIS FROM S-PHASE HISTONE SYNTHESIS IN DIVIDING CELLS.

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Cell; 27(2):321-330 1981

Histone synthesis in cycling tissue-culture cells can be separated into basal synthesis and S-phase synthesis. S-phase histone synthesis comprises about 90% of total histone synthesis, and in this regard our results support the generally held model that most histone synthesis is tightly linked to DNA synthesis. Basal histone synthesis is less than 10% of the S-phase synthesis but persists throughout the S, G2 and G1 phases of the cell cycle, while S-phase synthesis rises in parallel with the increase in DNA synthesis. Chinese hamster ovary cells, the H2A variants Z and X, and the H3 variant 3, participate in basal histone synthesis while the H2A variants 1 and 2, and the H3 variant 2, participate in S-phase histone synthesis. H2B and H4 participate in both kinds of synthesis. Because specific H2A and H3 variants are involved, basal histone synthesis cannot be attributed to contamination by cells in S-phase. Whole cells and isolated nuclei yield the same results. Basal histone synthesis can be demonstrated in cells synchronized by mitotic shake-off either alone or in combination with isoleucine starvation and colcemid blockage. It is also differentiated from S-phase histone synthesis by its relative insensitivity to hydroxyurea, indicating that basal histone synthesis is not linked or is at least less tightly linked to DNA synthesis. The basal H2A variants X and Z of five other cell lines all show similar relative insensitivities to hydroxyurea treatment. These lines include attached cultures, suspension cultures, a normal line and transformed lines from human, mouse, rat and Chinese hamster, indicating that basal histone synthesis may be a property of all cycling cells. The integration of basal histones into chromatin seems to follow the same pathway as S-phase histones, but the kinetics are somewhat slower. (Author abstract) (32 Refs)

68. EUCHROMATIN PROTEIN PHOSPHORYLATION AND NEOPLASTIC TRANSFORMATION (MEETING ABSTRACT).

DeLuca C, Smith GJ

Department of Pathology, University of New South Wales, New South Wales, Australia

Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Non histone chromosomal proteins (NHCP) are thought to have a specific gene regulatory function. Indentification and characterization of phosphorylated NHCP may provide useful cellular markers for the early onset of neoplasia and may elucidate mechanisms of neoplasia. The experiment design involves an analysis of euchromatin protein alteration during the initial and promotional stages of chemical carcinogenesis as outlined in the Solt-Farber regime. Diethylnitrosamine (DEN) is used as the initiating agent and promoting is achieved through the dietary administration of 2-acetylaminofluorene accompanied by a non-specific growth stimulus-partial hepatectomy. The DNAse I prepared soluble transcriptionally active (euchromatin) fraction is extracted from purified nuclei, labelled with [32P] orthophosphate in primary cell suspension culture. The chromatin proteins are analyzed by two dimensional polyacrylamide gel electrophoresis and autoradiography. Preliminary observations indicate that following a single dose of DEN (200 mg/kg ip), there is acute histological damage to nuclei at one wk and complete recovery within three wk. Electron micrographs of purified nuclei confirmed these findings. Furthermore, electrophoretic analysis of control and DEN treated animals using Coomassie blue visualization of proteins, resulted in the detection of several proteins, not evident in the control animals. (no Refs)

69. ABERRANT AND NONRANDOM METHYLATION OF CHROMOSOMAL DNA-BINDING PROTEINS OF COLONIC EPITHELIAL CELLS BY 1,2-DIMETHYLHYDRAZINE.

Boffa LC, Gruss RJ, Allfrey VG

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Cancer Res; 42(2):382-388 1982

The alkylating carcinogen 1,2-dimethylhydrazine (DMH) induces colonic tumors with high incidence. The sites of in vivo modification of target macromolecules were studied using [methyl-3H]DMH. Carcinogen binding to subcellular fractions of colonic epithelial cells was analyzed at time intervals ranging from 10 min to 36 hr, with particular emphasis on the alkylation of nuclear constituents. DMH modifies not only nucleic acids but also histones and other DNA-binding proteins in the target cells. Separation of the 3H-methylated amino acids showed aberrant methylation patterns after exposure to [3H]DMH, as compared with methylations observed with [methyl-3H]methionine as a natural methyl group donor. DMH-modified histone H1 contained methylated lysine, arginine, and histidine residues not normally found, and other histones had abnormal methylarginine contents. High-mobility-group proteins and other nuclear proteins contained methyllysine residues not normally detected. Proteins known to be associated with template-active and more accessible DNA sequences, such as the high-mobility group proteins and the multiacetylated forms of histones H3 and H4, were preferentially damaged after exposure to [3H]DMH. The result suggests that carcinogen-induced chromosomal damage is not random and may selectively affect proteins in the actively transcribing or replicating genes in the target cells. That damage affects the amino acids most likely to be involved in DNA binding. (Author abstract) (47 Refs)

70. TUMOR-ASSOCIATED CHROMATIN ANTIGENS OF HUMAN COLON ADENOCARCINOMA CELL LINES HT-29 AND LOVO.

Duhl DM, Banjar Z, Briggs RC, Page DL, Hnilica LS
Dept. Biochemistry, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232
Cancer Res; 42(2):594-600 1982

Antiserum to dehistonized chromatin from human colon adenocarcinoma cell line HT-29 was raised in rabbits and used for the immunodetection of colon tumor-associated nuclear antigens. Quantitative microcomplement-fixation studies indicated that the antiserum had reactivity similar to those of chromatins of two human colon adenocarcinoma cell lines (HT-29 and LoVo) and with nonneoplastic colon. Immunocytochemical localization showed the chromatin antigens to be evenly dispersed throughout the nucleus. Immunochemical staining of electrophoretically separated chromosomal proteins transferred to nitrocellulose sheets revealed several intensely staining antigens predominantly in the mol wt range of 62,000 to 75,000. When the antiserum was immunoabsorbed with nonneoplastic human colon chromatin, two antigens with mol wt of 67,000 and 92,000 were identified only with the tumor chromatins. Antiserum immunoabsorbed with either LoVo or HT-29 chromatin failed to show any immunoreactivity, suggesting that these tumor-associated proteins, or antigenic sites residing on these proteins, are identical in both colon tumor cell lines. (Author abstract) (43 Refs)

71. MOLECULAR MECHANISMS INVOLVED IN MORPHOLOGICAL VARIATION OF AVIAN SARCOMA VIRUS-INFECTED RAT CELLS.

Chiswell DJ, Enrietto PJ, Evans S, Quade K, Wyke JA
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Virology; 116(2):428-440 1982

Clones of avian sarcoma virus (ASV)-infected rat cells are heterogeneous, containing both morphologically transformed and morphologically normal cells. Morphological variation is reversible: normal cells can give rise to transformed daughters and they in turn can segregate morphologically normal revertants. However, reversion of transformed clones seems to occur more readily than transformation of normal cells. In most cases, morphologically normal cells contain recoverable viruses with no defect in transformation and yet the cells themselves are usually fully susceptible to transformation by superinfecting ASV. With one exception, morphological changes are not accompanied by detectable alterations in the size or chromosomal location of the single ASV provirus that these clones possess. In one clone, A11, that has been examined in detail, transformed segregants contain virus specific RNAs and the viral transforming protein, pp60src, whereas in normal subclones neither RNA nor protein can be detected. These results indicate that morphological variation reflects a reversible modulation in expression of viral functions, probably specific to individual proviruses and probably operating at the level of viral RNA transcription. (Author abstract) (33 Refs)

72. INTERACTION OF SV40 T-ANTIGEN WITH CHROMATIN IN TUMOR CELLS.

Rheszowska-Wolny I, Sadzinska L, Grobner S, Shliankevich MA, Drize OB, Demina EB, Polotskaia AV
Inst. Oncology, Gliwice, Poland
Biokhimiia; 46(10):1880-1886 1981

Sedimentation analysis and electrophoresis in the polyacrylamide gel showed the presence of T-antigen of simian virus SV40 in the chromatin isolated from SV40-induced Syrian hamster tumors. T-antigen was bound to oligonucleosomes fraction. It was suggested that T-antigen interacts not only with DNA but also with H1 histone. (24 Refs) (In RUS)

73. MAPPING THE IN VIVO ARRANGEMENT OF NUCLEOSOMES ON SIMIAN VIRUS 40 CHROMATIN BY THE PHOTOADDITION OF RADIOACTIVE HYDROXYMETHYLTRIMETHYLPSORALEN.

Robinson GW, Hallick LM
Dept. Biochemistry, Oregon Health Sciences Univ., Portland, OR, 97201
J Virol; 41(1):78-87 1982

Intracellular simian virus 40 (SV40) chromatin was photoreacted with a 3H-labeled psoralen derivative, hydroxymethyltrimethylpsoralen (HMT), at 48 hr postinfection. Psoralen compounds have been shown to readily penetrate intact cells and, in the presence of long-wavelength UV light, form covalent adducts to DNA, preferentially at regions unprotected by nucleosomes. The average distribution pattern of [3H]HMT on the SV40 genome was determined by specific activity measurements of the DNA fragments generated by HindIII plus HpaII or by AtuI restriction enzyme digestion. At levels of 1 to 10 [3H]HMT photoadducts per SV40 molecule, the radiolabel was found to be distributed nonrandomly. Comparison of the labeling pattern in vivo with that of purified SV40 DNA labeled in vitro revealed one major difference. A region of approx 400 base pairs, located between 0.65 and 0.73 on the physical map, was preferentially labeled under in vivo conditions. This finding strongly suggests that the highly accessible region near the origin of replication, previously observed on isolated SV40 'minichromosomes,' exists on SV40 chromatin in vivo during a lytic infection. (Author abstract) (66 Refs)

74. SIMIAN VIRUS 40 AS A PROBE FOR STUDYING INDUCIBLE REPAIR FUNCTIONS IN MAMMALIAN CELLS.

Mezzina M, Gentil A, Sarasin A
Institut de Recherches Scientifiques sur le Cancer, B.P. no 8, 94802 Villejuif C edex, France
J Supramol Struct Cell Biochem; 17(2):121-131 1981

Simian virus 40 (SV40) was used as a biological probe to examine inducible DNA repair pathways in monkey kidney cells in order to study the effect of pyrimidine dimer lesions on SV40 DNA replication, the induction of an error-prone replication process in DNA-damaged monkey cells, and the presence of recombinogenic activity in carcinogen-treated cells. Characteristics of viral replicative intermediate molecules made shortly after UV irradiation were studied in irradiated SV40-infected African green monkey cells. The tight homology between the size of newly synthesized DNA made after UV irradiation (40%), the av length of the tail measured in the same samples by electron microscopy analysis (41%), and the av distance between two pyrimidine dimers measured with the T4 endonuclease V (37%) suggested that the viral replication fork is blocked by a pyrimidine dimer leaving a single-stranded region in the opposite strand where an endonucleolytic cleavage may occur to generate the tail. Evidence for the induction of error-prone DNA replication is presented for SV40 cells in which DNA synthesis has been inhibited. An experimental protocol is proposed for the study of inducible recombination through the use of SV40 genetic markers. (36 Refs)

EFFECTS OF EXOGENOUS AGENTS ON CHROMOSOMES

75. X-RAY INDUCED CHROMOSOME ABERRATIONS IN DOWN LYMPHOCYTES: AN EXPLANATION OF THEIR INCREASED SENSITIVITY.

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Environ Mutagen; 3(1):85-89 1981

Association between altered repair of radiation-induced damage in lymphocytes from two individuals with Down syndrome (trisomy 21) compared with normal cells, and the involvement of the association in increasing chromosome aberration frequencies, were studied. Aberration frequencies in normal and Down lymphocytes were compared following x-irradiation and postirradiation incubation with cytosine arabinoside (ara-C), 5 x 10(-5) M, for 0, 0.5, 1 or 2 hr. Unstimulated Down lymphocytes are more sensitive to the induction of dicentric and ring aberrations by x-rays than normal lymphocytes. X-irradiated cells incubated with ara-C exhibited large increases in aberration frequencies which were proportional to length of exposure to ara-C. Results suggest that the initiation of the repair of damage which is converted into chromosome aberrations is more rapid in Down cells than in normal cells. This could be explained if the total amount of DNA damage which can be converted int aberrations is the same in both cell types but the repair is more rapid in Down cells. Results explain the increased sensitivity of unstimulated lymphocytes from individuals with Down syndrome to the induction of dicentrics by x-rays. The more rapid repair of Down cells results in a higher probability of producing chromosome aberrations and higher aberration frequencies in Down than normal cells. (5 Refs)

76. ELIMINATION OF RADIATION-INDUCED CHROMOSOME ABERRATIONS IN A CULTURE OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES. I. FREQUENCY OF ABERRATIONS IN THE FIRST AND IN THE SECOND MITOSES.

Piatkin EK, Nugis VIu
Inst. Biophysics, Moscow, USSR
Tsitologiia; 23(11):1310-1316 1981

The frequency of radiation-induced chromosome aberrations was studied in human peripheral blood lymphocytes irradiated with 60Co gamma rays (100-500 rads). Irradiated cells were incubated with broxuridine for 58-66 hr, and the chromosome aberrations in the first and second mitoses were assessed by the harlequin staining. For all radiation dosages tested, the frequency of chromosome aberrations in the first mitosis was 1.6-2x greater than that in the second mitosis. (15 Refs) (In RUS)

77. ACTIVATED OXYGEN SPECIES AT THE ORIGIN OF CHROMOSOME BREAKAGE AND SISTER-CHROMATID EXCHANGES.

Emerit I, Keck M, Levy A, Feingold J, Michelson AM
Laboratoire de Cytogenetique Experimentale, Institut Medical des Cordeliers, Universite Paris VI, 15, Rue de l'Ecole de Medecine, Paris 6eme, France
Mutat Res; 103(2):165-172 1982

The effect of free superoxide anion radicals produced by the xanthine oxidase system in causing chromosome breaks and rearrangements, plus increased sister chromatid exchanges (SCE), in human lymphocytes is compared with the results of those produced by photoreduction of flavine mononucleotide by near-UV radiation. The protective influence of superoxide dismutase (SOD) was also tested. Both methods of free radical generation caused chromosome aberrations, mainly chromatid breaks (50%) and gaps (28%), and SCE, which could be prevented with SOD. (22 Refs)

78. PRENEOPLASTIC FOCI IN BABY MOUSE DERMIS CULTURES (MEETING ABSTRACT).

Cooper P, Marshall S, Masinello G
Department of Microbiology, John Curtin School of Medical Research, Australian National University, Canberra, Australia
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

The preneoplastic process is being explored by inducing, within 10-14 days, altered cell foci upon exposure of dermis cells from 24 hr old C57 black mice to this light and/or 10(-6) M colchicine. These treatments greatly enhance focus formation. The foci have characters resembling neoplastic cells and overgrow the density-inhibited monolayers from which they arise; however, cell lines isolated from them, although aneuploid, do not form colonies in soft agar or tumors in syngeneic mice and are regarded as preneoplastic. The cells pass through DNA synthesis in presence of colchicine, and prevention of DNA synthesis by low serum or hydroxyurea greatly decreases focus formation. Flow cytofluorimetry shows that greater than 50% of cells become arrested in 4n chromosome configuration in presence of colchicine, and immediately after removal of the drug 10-20% of the cells replicate in this configuration to form 8n and higher chromosome numbers, with a spread of intermediate values. Stained cultures reveal many abnormal nuclear divisions, yielding 2 to 6 daughter nuclei or unequal sizes; colony forming ability at this time is 10(-5)-10(-6), the cultures passing through a 'crisis'. Protein synthesis revealed by PAGE (polyacrylamide gel electrophoresis) shows little difference in overall gene expression between parental cells and preneoplastic clones. A search for a more specific analysis revealed that glycoproteins isolated from the clones by Sepharose-Concanavalin A affinity chromatography differed noticeably from parental cells. (no Refs)

79. SISTER CHROMATID EXCHANGE FREQUENCY IN HUMAN EPIDERMAL CELLS IN CULTURE TREATED WITH 8-METHOXYPSORALEN AND LONG-WAVE UV RADIATION.

West MR, Johansen M, Faed MJ
Cytogenetics Lab., Dept. Pathology, Ninewells Hosp. and Medical Sch., Dundee, DD1, 9SY, Scotland
J Invest Dermatol; 78(1):67-68 1982

The effects of 8-methoxypsoralen with long-wave ultraviolet radiation on the sister chromatid exchange frequency in human epidermal cells in culture was investigated. With a constant amount of radiation the number of exchanges increased in an approx linear manner with increasing concentrations of 8-methoxypsoralen up to 0.3 ug/ml. Above this concentration there were fewer dividing cells and an apparent departure from linearity in the dose-response curve. These results show that 8-methoxypsoralen concentrations equivalent to those found in the serum of patients undergoing photochemotherapy, in conjunction with UVA radiation, cause striking increases in sister chromatid exchange frequency in human epidermal cells in vitro. (Author abstract) (21 Refs)

80. CYTOGENETIC ANALYSES OF LYMPHOCYTES FROM WORKERS IN A NICKEL REFINERY.

Waksvik H, Boysen M
Dept. Genetics, Norwegian Radium Hosp., Oslo 3, Norway
Mutat Res; 103(2):185-190 1982

Chromosomal aberrations (gaps, breaks, exchanges) and sister-chromatid exchanges (SCE) in the lymphocytes of two groups of refinery workers exposed to 0.5 or 0.2 mg Ni/cubic meter (m3) of air were compared with those of a similar group made up of office workers from the same company. The 0.5 and 0.2 mg Ni/m3 refinery groups had higher blood plasma Ni concentrations and significantly increased numbers of chromosomal gaps than the control workers (11.9% and 18.3% vs 3.7%). The difference in percentage of gaps between the two worker groups was not statistically significant. No significant relation between the increase in gaps and plasma Ni concentration, duration of exposure, or subject age was found. Break percentages did not differ significantly from those of controls, and no exchanges were found. SCE levels did not differ significantly among groups. A potential genetic hazard from nickel refinery processes is suggested, but some environmental aspects of exposure, such as other metals in the workplace, were not ruled out in this study. (19 Refs)

81. NORMAL SISTER-CHROMATID EXCHANGES IN ORAL CONTRACEPTIVE USERS.

Husum B, Wulf HC, Niebuhr E
Dept. Anaesthesia, Rigshospitalet, Copenhagen, Denmark
Mutat Res; 103(2):161-164 1982

A group (A) of 63 women (15-42 yr old; av 22.3) who used no medication whatsoever was compared with a second group (B) of 52 women (16-43 yr old; av 26.3) who used oral contraceptives (OC; combinations of progestins and estrogens) with respect to the effect of cigarette smoking on sister chromatid exchanges (SCE) in peripheral lymphocytes. Mean numbers of SCE/cell ranged from 8.42-9.52 for group A, and 8.54-10.36 for group B, over a range of cigarette use of 0-greater than 20/day. The total number of SCE in 30 metaphases of each woman was transformed from an assumed Poisson distribution to a normal distribution, and a linear regression and Bartlett's test were performed which gave independent estimates of basic variance summed as 4.43 for group A and5.97 for group B. It was concluded that use of OC does not influence SCE in lymphocytes in either smoking or nonsmoking women. (8 Refs)

82. INDUCTION OF SISTER-CHROMATID EXCHANGE IN HUMAN LYMPHOCYTES BY SMOKE CONDENSATES FROM DIFFERENT BRANDS OF CIGARETTE.

Sorsa M, Norppa H, Leppanen A, Rimpela M
Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Mutat Res; 103(2):149-153 1982

The mutagenic activities of smoke condensates (SC) from six commercially available cigarette brands were evaluated by sister-chromatid exchange (SCE) analysis of cultured human lymphocytes. Extracts of SC dissolved in dimethyl sulfoxide (DMSO; 25 mg tar/ml) were added to cultures to yield final concentrations of 50, 100, and 200 ul/ml of culture, and matching controls with DMSO were included. All six SC induced SCE; the highest concentration inhibited cell division in all samples. Results suggest that the amount of tar in cigarettes and the number of cigarettes smoked may affect the mutagenic potency of the resulting SC. (13 Refs)

83. MUTAGENICITY STUDIES ON BUFEXAMAC.

Fabry L, Leonard A, Decat G, Roba J

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Mutat Res; 103(2):107-109 1982

The ability of bufexamac (p-butoxyphenylacethydroxamic acid; BF) and/or its metabolites to induce sister-chromatid exchanges (SCE) was determined in human lymphocytes. Treatments of 24 hr without, or 1 hr with, liver enzyme activation produced no statistically significant increase in SCE at BF concentrations of 5 x 10(-4), 10(-4), 10(-5) M, compared to treatment with dimethylsulfoxide. (13 Refs)

84. INHIBITORY EFFECT OF INTERFERON ON MMC INDUCED SISTER CHROMATID EXCHANGES (MEETING ABSTRACT).

Ide T, Maekawa T, Edagawa J, Taniwaki M, Sonoda Y, Misawa S, Abe T, Takino T, Kishida T

Department of Medicine and Department of Microbiology, Kyoto Prefectural University of Medicine, Kyoto, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp , 1981.

Effect of human lymphocyte interferon (IF) on the frequency of sister chromatid exchange (SCE) was examined. IF itself showed no increase of SCEs in the human lymphocyte culture. Mitomycin C (MMC) (2x10-8M) induced 11.6 SCEs/cell. In the culture containing 200 u/ml of IF, MMC induced 9.6 SCEs. The control level of SCEs in the IF and MMC free culture was 5.1. Results indicated that IF has a inhibitory effect of MMC induced SCEs in vitro. (no Refs)

85. MUTAGENIC ACTIVITY OF TOMIZINE.

Gvazava EA, Revazova IuA, Radchenko LU, Bratslavskii VA, Oblapenko NG, Bobrinev EV

Res. Inst. Biological Testing of Chemical Compounds, Moscow Oblast', USSR

Khim Farm Zh; 15(11):31-34 1981

The activity of the antineoplastic agent tomizine (folic acid antagonist) was studied by means of various mutagenicity tests. The tomizine did not induce gene mutations in Salmonella, but increased the frequency of recessive lethal mutations in Drosophila. Exposure of male mice to the agent increased the frequency of dominant lethal mutations (15.5%, compared with 3.9% in control mice). The tomizine did not induce sister chromatid exchanges in human peripheral blood lymphocytes. (16 Refs) (In RUS)

86. STARVATION OF ARGININE AND GLUTAMINE SENSITIZES HUMAN DIPLOID CELLS TO THE TRANSFORMING EFFECTS OF N-ACETOXY-2-ACETYLAMINOFLUORENE.

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Carcinogenesis; 2(12):1303-1310 1981

We have examined the influence of the method of synchronization on the transformation of normal human diploid fibroblasts treated in mid-S phase with N-acetylaminofluorene (N-Ac-AAF), and on the subsequent kinetics of the removal of carcinogen damage. At early times posttreatment, the transformation frequency in cultures synchronized by a 24 hr starvation for arginine and glutamine was enhanced over that of cultures synchronized by release from confluence. In cells synchronized by either method, transformation was enhanced at all times when the cells were incubated after treatment in medium containing high concentrations of nonessential amino acids, vitamins and serum. Synchronized cells treated with 3 uM [3H]N-Ac-AAF in mid-S removed significantly less DNA damage than cultures treated and held under confluent, noncycling conditions. Cells synchronized by amino acid starvation removed less damage than cells synchronized by release from confluence. S-phase treatment of synchronized cells resulted in a dose-dependent delay of DNA replication. The early, rapid phase of repair was temporally correlated with the delay in S-phase progression. We conclude from these data that synchrony achieved by amino acid starvation renders human cells more sensitive to N-Ac-AAF-induced transformation in vitro than does that achieved by release from density-inhibition of growth. The S-phase treated, cycling cells lost only about 10% of their initial carcinogen damage before reinitiation of treatment-delayed bulk DNA synthesis. These results support the hypothesis that the persistence of carcinogen damage in replicating DNA may be an important factor in cell transformation. (Author abstract) (46 Refs)

87. INDUCTION OF SISTER CHROMATID EXCHANGES IN HUMAN DIPLOID FIBROBLASTS BY MUTAGENS WITH AND WITHOUT RAT LIVER MICROSOMAL ACTIVATION.

Yang DP, Graupensperger F, Minecci LC, Rubin BA
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Environ Mutagen; 3(1):45-52 1981

Effects of a promutagen, a plant clastogen, and two direct mutagens were tested on sister chromatid exchange (SCE) induction in WI-38 cells with and without rat liver microsomal activation. Exponentially growing cells, 24 hr after subcultivation were treated with cyclophosphamide (CY), maleic hydrazide (MH), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), and 4-nitro-quinoline-1-oxide (4NQO) at various concentrations in the growth medium at 37 C for 1 hr. The frequency of SCE was estimated by the 5-bromodeoxyuridine-dye technique with and without addition of rat liver microsomal suspension (S-9). CY concentrations from 1 x 10(-5) M to 1 x 10(-3) M with S-9 mix increased the number of SCE/cell in a dose-dependent manner. Without S-9 mix, CY concentrations less than 1 x 10(-3) M did not produce more SCE than the controls. MNNG at 1 x 10(-8) M and 4NQO at 1 x 10(-7) M without S-9 produced significant increases in SCE/cell. Addition of S-9 slightly decreased the effects of MNNG and 4NQO in the formation of SCE. MH was tested at pH 6.4 and pH 7.6. MH at 1 x 10(-3) M without S-9 mix inhibited cell multiplication at pH 7.6, but did not cause a significant increase in SCE/cell. No interactions were noted between MH (2 x 10(-4) M) and S-9 mix nor between MH and pH levels tested. Results indicate that in the presence of metabolic activation, SCE formation in human diploid fibroblasts in vitro may be used as a potential assay for mutagenicity. (35 Refs)

88. COMPARISON OF THE FREQUENCIES OF SCES INDUCED BY CHEMICAL MUTAGENS IN BONE-MARROW, SPLEEN AND SPERMATOGONIAL CELLS OF MICE.

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Centro di Studio di Genetica Evoluzionistica del Consiglio Nazionale, delle Richerche Istituto di Genetica, Universita di Roma, Piazzale delle Scienze 5, 1-00185 Roma, Italy

Mutat Res; 103(2):191-195 1982

Dose-effect curves are described for the incidence of sister chromatid exchanges (SCE) in Swiss mouse bone marrow, spleen, and spermatogonial cells previously treated in vivo with chemical mutagens (methyl methanesulfonate [MMS]; mitomycin C [MMC]; cyclophosphamide [CP]; 4-nitroquinoline oxide, [4NQO]; bleomycin [BLE]) to evaluate the relative sensitivity of the cell types to SCE-induction by each mutagen. Spontaneous SCE levels were the same for the three cell types, and SCE levels induced by mutagens were similar in the bone marrow and spleen cells, but were significantly less in spermatogonial cells. Mutagen effects on SCE were concentration-dependent, but not linear, suggesting detoxification by the cells at lower doses, even with MMS, which does not require metabolic activation. CP and MMC were efficient mutagens but 4NQO and BLE were not. Spermatogonial cells were evidently better protected against mutagens than the other cells. The SCE method should allow reliable comparison of mutagen sensitivities between somatic and germinal tissues. (17 Refs)

89. CHROMOSOME-BREAKING ABILITY OF ARECOLINE, A MAJOR BETEL-NUT ALKALOID, IN MOUSE BONE-MARROW CELLS IN VIVO.

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Mutat Res; 103(2):197-204 1982

Arecoline (1,2,5,6-tetrahydro-1-methyl-3-pyridine carboxylic acid methyl ester), an ingredient of betel-quid, which is chewed commonly in Southeast Asia and the Western Pacific and has been associated with a high rate of oral cancer in these areas, was tested for in vivo chromosome breaking ability with Swiss albino mouse bone marrow. Commercial arecoline was administered by daily ip injection at concentrations of 2.0, 1.0, 0.5, and 0.25 mg per mouse and given for 10, 20, and 30 days for each dose. Aberrations in metaphase chromosomes were greatest at higher doses, and included chromatid and chromosome breaks, ring structures, multiple breaks, and pulverization of chromosomal elements. There was an inverse relationship between the duration of arecoline exposure (10, 20, or 30 days) and the magnitude of chromosome aberrations, which gradually declined as treatment time increased. Chromatid breaks was the only damage noted in control cells, which were treated with vehicle. (24 Refs)

90. SODIUM PENTOBARBITAL-INDUCED MUTATIONS IN THE HAMSTER.

Ito T, Ingalls TH
(c/o Ingalls) Epidemiology Study Center, 25 Deloss St., Framingham, MA, 01701
Arch Environ Health; 36(6):316-320 1981

When virgin Syrian hamsters aged 6 to 8 wk were mated during estrus and anesthetized with sodium pentobarbital (Nembutal) 4 to 5 hr before estimated ovulation, pregnancy wastage in the newly conceived litter was observed. This was manifested by polyspermy of moribund eggs and death of fertilized eggs, deficits of expected zygotes, and triploidy and tetraploidy in 3-day-old surviving embryos. Multiple factors determined the nature of this wastage, including dosage of Nembutal [sodium 5-ethyl-5-(1-methyl butal) barbiturate], route of its administration, degree of resulting respiratory depression, and ultimately a pH imbalance (below 7) in the mother. Polyspermy appeared to result from the penetration of degenerating ova by 10-20 sperm, triploidy to polar body retention, and tetraploidy to endoreduplication of chromosomes before cell cleavage; identification of 2N/4N mosaics supports this inference. (Author abstract) (11 Refs)

91. EFFECT OF POST-TREATMENT WITH APHIDICOLIN - A SPECIFIC INHIBITOR OF DNA POLYMERASE ALPHA - ON SISTER-CHROMATID EXCHANGES INDUCED BY ETHYL METHANESULFONATE.

Nishi Y, Hasegawa MM, Inui N, Ikegami S, Yamada MA
Biological Res. Center, Japan Tobacco and Salt Public Corporation, Hatano, Kanagawa 257, Japan
Mutat Res; 103(2):155-159 1982

The effect of post-treatment with aphidicolin (AP) on sister-chromatid exchanges (SCE) induced by ethyl methanesulfonate (EMS) was determined in V79 cells. AP at 200 nanog (ng)/ml is toxic to V79 cells, but about half that amount does not affect survival appreciably; treatment did not affect colony size. In the absence of AP, EMS induced SCE in a linear, dose-dependent manner. With 80 ng/ml AP present during the post-treatment (for 2 rounds of replication) SCE were enhanced (1.8x controls) in groups pretreated with EMS (100-400 ug/ml), but not in controls pretreated with dimethyl sulfoxide. AP at 8 ng/ml during post-treatment caused slight, but not significant, increase in SCE; 800 ng/ml AP prevented cell cycle completion. The presence of AP is thought to have increased the effectiveness of EMS in induction of SCE, rather than to have caused SCE directly, since AP alone was without. (24 Refs)

92. INTERINDIVIDUAL VARIATION OF CARCINOGEN ACTIVATION BY HUMAN LIVER HOMOGENATES: A STUDY USING DIMETHYLNITROSAMINE (DMN) AND CYCLOPHOSPHAMIDE (CP) AS PRECURSOR GENOTOXIC AGENTS AND CLASTOGENICITY AND INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER V79-E CELLS AS ENDPOINTS.

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Arch Geschwulstforsch; 52(2):97-104 1982

Interindividual variation in activation of carcinogens by liver homogenates (LH) from six kidney donors was studied. Liver tissue was homogenized and centrifuged at 9,000 gravities. Similar LH were made from livers of inbred rats of strain E. Mixtures of LH supernatants (S-9) and exponentially growing, asynchronous Chinese hamster V79-E cells were exposed to dimethylnitrosamine (DMN) or cyclophosphamide (CP) for 3 hr. Human S-9 alone produced no abnormalities in V-79-E cells. With 10(-2) DMN human S-9 produced 43.7% abnormal metaphases (AM), with a 1.3-fold variation among individuals; 3.46 sister chromatid exchanges (SCE)/chromosome were produced, with a 1.3-fold variation. With the same level of DMN, rat S-9 produced 35% AM and 3.58 SCE/chromosome. With 10(-3) M CP human S-9 produced AM ranging from background levels to complete cell killing; SCE ranged from 1.33-7.35/chromosome. With 10(-4) M CP, rat S-9 produced 16% AM and 2.82 SCE/chromosome. With 10(-3) M CP, rat S-9 produced total cell killing. Results indicate that human LH activate DMN to approx the same extent as rat LH, but that activation of CP by human LH is much more varied. (33 Refs)

93. 2,4-DICHLOROPHENOXYACETIC ACID - A NEW ENVIRONMENTAL MUTAGEN.

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Post-Graduate Dept. Botany, Nagpur Univ. Campus, Nagpur 440 010, India
Mutat Res; 103(2):111-114 1982

The mutagenic and teratogenic potential of 2,4-dichlorophenoxyacetic acid (2,4-D) were tested on barley (Hordeum vulgare) seeds at a concentration of 100 ppm. The compound did not affect markedly seedling height, but reduced germination and seed set. Other effects on the M1 generation included increased chromosomal aberrations, increased chlorophyll chimeras, and increased aberrant pollen mother cells and sterile pollen. In the M2 generation the chlorophyll-deficient mutations albina, viridis, chlorina, tigrina, striata, alboviridis, and viridoalba occurred, with tigrina types dominant (58-61%). While the mutagenic properties of 2,4-D demonstrated are potentially useful to breeders, caution is suggested in its use as an herbicide or hormone. (15 Refs)

94. ANTIPAIN AND RADIATION EFFECTS ON ONCOGENIC TRANSFORMATION AND SISTER CHROMATID EXCHANGES IN SYRIAN HAMSTER EMBRYO AND MOUSE C3H/10T1/2 CELLS.

Geard CR, Rutledge-Freeman M, Miller RC, Borek C
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Carcinogenesis; 2(12):1229-1233 1981

Depending on its time of addition to Syrian hamster embryo or mouse C3H 10T1/2 cells the protease inhibitor antipain (AP) can enhance, or reduce, radiation induced-oncogenic transformations. These opposing influences are not paralleled by changes in sister chromatid exchanges in either cell system. A 24 hr treatment with 10 uM AP prior to, and during irradiation, with removal 10 min after irradiation results in greater than a two-fold increase in transformants. Conversely, a 24 hr treatment beginning 10 min after irradiation results in about a two-fold decrease in transformants. The utility of AP as an agent for the reduction of tumorigenesis is brought into question, since quite short temporal differences in application can result in near five-fold differences in the frequencies of oncogenic transformations. (Author abstract) (32 Refs)

95. 5-BROMODEOXYURIDINE SUBSTITUTION AND DIFFERENTIAL RADIOSENSITIVITY OF UNI- AND BI-FILAR CHROMATIDS.

Jacob M
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Mutat Res; 103(2):173-176 1982

Further data are supplied to support the observation that differential radiosensitivity of uni- and bi-filarly 5-bromodeoxyuridine (BrdU)-substituted chromatids in muntjac lymphocytes was real, and not an artifact of BrdU depletion during the second cycle as suggested recently by Wolff and Fijtman. Heparinized whole blood of a female muntjac was cultured in supplemented Parker TC199 medium; after growth of cultures, the medium was harvested and reused in order to assess the effect of BrdU depletion on cell cycle progress. Metaphase percentages in 48 hr normal cultures of muntjac lymphocytes with 1 ug/ml (3 uM) BrdU were 40, 47, and 13 in cycles I, II, and III, respectively. With reuse of the same medium, the respective percentages were 60, 36, and 4. Thus, the muntjac lymphocytes were able to continue the cell cycle at BrdU levels considered inadequate as reported by Wolff and Fijtman for CHO cells. The data confirm that the dark and light chromatids reported earlier are actually uni- and bi-filarly substituted. (7 Refs)

GENERAL REVIEWS

96. PHILADELPHIA CHROMOSOME (PH1)-POSITIVE ACUTE MYELOGENOUS LEUKEMIA: TWO AUTOPSIED CASES AND A REVIEW OF THE LITERATURE.

Musashi M, Katahira J, Kurane R, Ono S, Miyazaki T, Okada M, Imai M, Kajita A
Section Hematology, First Dept. Medicine, Tokyo Women's Medical Coll., Tokyo, Japan
Rinsho Ketsueki; 22(6):832-843 1981

Two male patients (69 and 60 yr old) with Philadelphia chromosome (Ph1)-positive acute myelogenous leukemia (AML) are described. Both patients presented with leukocytosis. Neither splenomegaly or basophilia were observed. Marked proliferation of blasts in bone marrow and peripheral blood was noted. Blasts were peroxidase- and Sudan black B-positive. Hypodiploidy with Ph1 was found in most metaphases of bone marrow cells. The karyotypes were [45, XY,-7, t(9;22)] and [45, XY,-18, 7t(9; 22)], respectively. Ph1-positive AML was diagnosed. Combination chemotherapy (vincristine, cytosine arabinoside, 6-mercaptopurine, and prednisolone) induced a 10-wk complete remission in one patient; the patient died 7 mo after diagnosis. During remission no characteristic feature of chronic myelogenous leukemia were observed. The other patient died 4 mo after diagnosis. Features characteristic of Ph1-positive AML, as obser ved in 31 cases from the literature, include: lack of marked splenomegaly and basophilia, mosaic of Ph1-positive and -negative cells, occasional disappearance of Ph1-positive cells during remission, high incidence of an unusual translocation of Ph1, and characteristic additional chromosomal aberrations. (73 Refs) (In JPN)

97. HUMAN CELL HYBRIDS: ANALYSIS OF TRANSFORMATION AND TUMORIGENICITY.

Stanbridge EJ, Der CJ, Doersen CJ, Nishimi RY, Peehl DM, Weissman BE, Wilkinson JE
Dept. Microbiology, Coll. Medicine, Univ. California, Irvine, CA, 92717
Science; 215(4530):252-259 1982

Intraspecific human-human cell hybrids provide a stable model system with which to investigate the genetic control of transformed and tumorigenic phenotypes. Using this system it has been shown that these phenotypes are under separate genetic control. Furthermore, the tumorigenic phenotype can be complemented by fusion of different tumorigenic cells, resulting in nontumorigenic hybrids. This system also provides information on the control of differentiated function. Molecular cytogenetic techniques should reveal the nature of the chromosomal control of neoplastic transformation. (Author abstract) (47 Refs)

98. CYTOGENETIC ANALYSIS IN HUMAN BONE MARROW TRANSPLANTATION.

Sparkes RS
Div. Medical Genetics, Dept. Medicine, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
Cancer Genet Cytogenet; 4(4):345-352 1981

Chromosome and sex chromatin studies have contributed significantly to the evaluation of human bone marrow transplants. In addition to their use in documenting bone marrow engraftment following transplantation, they have been used to (1) evaluate whether recurrent leukemia occurs in donor or recipient cells and whether recovery in aplastic anemia results from growth of host or donor cells, (2) demonstrate the bone marrow origin of pulmonary macrophages and hepatic Kupffer cells, (3) show that bone marrow fibroblasts have an origin different from that of the hematopoietic bone marrow cells, (4) evaluate twin zygosity in preparation for transplantation, and (5) show that the defect in Fanconi's anemia is intracellular. (Author abstract) (32 Refs)

99. ABORTIONS AND HYDATIDIFORM MOLES: THE GENETIC ASPECT.

Toaff R
No affiliation given
Harefuah; 101(5/6):120-122 1981

Chromosomal abnormalities underlying spontaneous abortions and hydatidiform moles are reviewed. Various authors have stated that the percentage of spontaneous abortions caused by a triploid number of chromosomes is between 5% and 15%. Seventy percent of pregnancies undergoing hydropic degeneration have a triploid chromosomal complement. However, only 13% of hydatidiform moles are triploid. Ninety percent of hydatidiform moles have what appears to be a normal female Karyotype (46 XX). Partial moles t end to be triploid and may be distinguished by focal trophoblastic hyperplasia. When a pregnancy appears to terminate because of a partial mole, checking the karyotype and determining that it is triploid may obviate the need to follow human chorionic gonadotropin levels and to consider chemotherapy. In the case of complete moles with seemingly normal karyotypes, studies with genetic markers have demonstrated that all the chromosomes are derived from a haploid paternal gamete. (22 Refs) (In HEB)

100. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.

Weinstein IB

Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032

J Supramol Struct Cell Biochem; 17(2):99-120 1981

Fundamental research at the cellular and molecular levels on mechanisms of action of chemical carcinogenesis and applied aspects and the concept of 'molecular epidemiology' of cancer are reviewed. The action of initiating agents and their metabolism and covalent binding to macromolecules is discussed under the following headings: metabolic activation, carcinogen potency, structures of carcinogen-DNA adducts, conformational changes in DNA, carcinogen modification of mitochondrial DNA, DNA repair, and carcinogen-DNA modification and mechanism of initiation. Tumor promotion and multifactor interactions are discussed in relation to two-stage skin carcinogenesis. Numerous effects elicited by phorbol ester tumor promotors, particularly 12-O-tetradecanoyl-phorbol-13-acetate, are classified into three categories: mimicry of transformation, modulation of differentiation, and membrane effects. Also considered in relation to phorbol ester tumor promotors, tumor promotion, and multifactor interactions are phorboid receptors, ion flux, possible role of kinases, chromosomal effects and activated oxygen, and chemical-viral interactions. The tumor-promoting activity of polycyclic aromatic hydrocarbons is discussed. A unified theory of tumor initiation and promotion is presented. Molecular epidemiology and cancer prevention are discussed with regard to limitations of current approaches and molecular cancer epidemiology. (94 Refs)

☆ U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/119

OTHER RELATED STUDIES

101. POISSON GOODNESS-OF-FIT TESTS FOR RADIATION-INDUCED CHROMOSOME ABERRATIONS.

Merkle W
Institut fur Strahlenschutz, Gesellschaft fur Strahlen- und Umweltforschung, D-8042 Neuherberg, W. Germany
Int J Radiat Biol; 40(6):685-692 1981

Asymptotic and exact Poisson goodness-of-fit tests have been reviewed with regard to their applicability in analyzing distributional properties of data on chromosome aberrations. It has been demonstrated that for typical cytogenetic samples, ie when the av number of aberrations per cell is smaller than one, results of asymptotic tests, especially of the most commonly used u-test, differ greatly fr om results of corresponding exact tests. While the u-statistic can serve as a qualitative index to indicate a tendency towards under- or over-dispersion, exact tests should be used if the assumption of a Poisson distribution is crucial, eg in investigating induction mechanisms. If the main interest is to detect a difference between the mean and the variance of a sample it is furthermore important to realize that a much larger sample size is required to detect under-dispersion than it is to detect over-dispersion. (Author abstract) (20 Refs)

102. EFFECT OF CAFFEINE ON CELL KILLING, MUTATION INDUCTION, DNA REPAIR, AND DNA SYNTHESIS AFTER TREATMENT WITH ETHYLNITROSOUREA.

Goth-Goldstein R, Painter RB
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Carcinogenesis; 2(12):1267-1271 1981

The effect of caffeine on cell killing, mutation induction, DNA repair, and inhibition of DNA synthesis was investigated in a clonal derivative of M3-1 Chinese hamster cells after treatment with N-ethyl-N-nitrosourea (ENU). Caffeine enhanced cell killing but had no effect on the mutation frequency/ viable cells for the two genetic markers, 6-thioguanine resistance and ouabain resistance. The removal of ethylated purine bases from DNA was as follows: most of the 3-ethyladenine was lost in 20 hr (greater than 85%) and approx 45% of the 7-ethylguanine was lost in 45 hr, whereas 75-93% of the O6-ethylguanine was still present at this time. Caffeine did not seen to influence these rates significantly. The ENU-induced inhibition of DNA synthesis was reversed by caffeine. It is concluded that the potentiation of ENU-induced cell killing by caffeine is caused by the increased frequency of DNA replication past damaged sites in parental DNA. (Author abstract) (25 Refs)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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CLINICAL STUDIES OF CHROMOSOMES IN HUMAN CANCER

1. CYTOGENETIC STUDIES IN 56 CASES WITH PH(1)-POSITIVE HEMATOLOGIC DISORDERS.

Lessard M, Le Prise PY
Laboratoire d'Hematologie, C.H.U. De La Miletrie, B.P. 577, 86021 Poiters, France
Cancer Genet Cytogenet; 5(1):37-49 1982

Karyotypes were examined in 56 cases of Ph(1)-positive hematologic disorders based on direct examination of bone marrow material and culture of blood for 24 hr without phytohemagglutinin (PHA). Various banding techniques (Q, followed by R or C, where necessary) were used. The series of patients consisted of 21 females and 35 males with the ages ranging from 3 to 72 yr. In three cases, the clinical and hematologic picture at the time of diagnosis and karyotyping was not compatible with chronic myeloid leukemia (CML): one case had acute myeloblastic leukemia (AML), another acute lymphoblastic leukemia (ALL) and the third subacute myeloid leukosis. The results are as follows: In three cases (2 females, 1 male), no Ph1 translocation could be demonstrated in any of the metaphases either with Q- or R-banding. In 50 cases (19 female, 31 male), a standard Ph1 translocation, t(9;22)(q34;q11), was observed. In two of these cases, ages 45 and 47, the Ph1 translocation was accompanied by loss of the Y chromosome in all the metaphases examined. Finally, in three cases (all male), variant Ph(1)-translocations were found: t(7;9)(9;22)(q35?;q31?;q11), t(3;9;22)(p21;q34;q11), and t(1;9)(9;22)(q21;q34;q11). (Author abstract) (21 Refs)

2. PHENOTYPIC CHANGES IN A CASE OF BLAST CRISIS OF CML: CHARACTERIZATION BY TDT, CYTOCHEMISTRY, AND CYTOGENETICS.

Paietta E, Schwarzmeier JD
First Medical Dept., Univ. Vienna Medical Sch., Lazarettgasse 14, A-1090 Vienna, Austria
Scand J Haematol; 27(4):241-246 1981

Phenotypic changes in blast crisis of a case of Philadelphia chromosome (Ph1)-positive chronic myelogenous leukemia were characterized by serial terminal transferase (TdT) determinations simultaneously related to cytochemical and cytogenetic data. At the onset of the blast crisis, 90% of the blast cells were acid phosphatase-positive (focal pattern), Ph1-positive, lymphoid cells. The TdT activity amounted to 29 units/10(8) mononuclear cells in the peripheral blood and to 57 units/10(8) mononuclear cells in the bone marrow. Therapy with vincristine and prednisone caused the elimination of the TdT-positive cell population. Four mo later, there was an increase in TdT-negative, myeloid blasts which was brought under control with busulfan. Cytogenetic analysis of the myeloid blasts still revealed Ph1 positivity in 100% of the metaphases examined and the lack of additional chromosomal abnormalities. A second relapse was again dominated by TdT-containing cells with the 46,XX,Ph1 karyotype. This time, the patient failed to achieve remission with vincristine and prednisone. Even though the TdT activity was markedly decreased, the lymphoid blast count remained elevated and the cells showed resistance to further therapy. This failure of morphology, cytochemistry as well as cytogenetics to distinguish between the individual phenotypes emerging during the course of blast crisis of CML characterized the TdT as a cell marker of important diagnostic and therapeutically prognostic value. (Author abstract) (17 Refs)

3. MYELOBLASTOMA AND ACUTE MYELOGENOUS LEUKEMIA: PRESENTATION WITH A CERVICAL NEUROPATHY AND COMPLETE RESPONSE TO CHEMOTHERAPY.

Mazur EM, Bertino JR
Mary Imogene Bassett Hosp., Cooperstown, NY, 13326
Cancer; 49(4):637-639 1982

Myeloblastoma is an uncommon complication of acute and chronic myelogenous leukemia. This is a report of a 25-yr-old man who was seen with simultaneous acute myelogenous leukemia (AML) and a myeloblastoma involving right-sided C7 and C8 nerve roots. The myeloblastoma, visible as a left apical mass on chest radiogram, resolved completely after 6 days of intensive AML induction chemotherapy. The patient subsequently had a complete remission with total resolution of all neurologic deficits. He remains in remission now 2 1/2 yr after initial diagnosis. An abnormal karyotype was present initially which became normal following chemotherapy. This case is an unusual example of myeloblastoma with peripheral nerve involvement. It illustrates that complete and durable resolution of these myeloblastic tumors can be achieved by intensive chemotherapy alone. (Author abstract) (11 Refs)

4. DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF CHROMOSOME ABNORMALITIES IN MARROW AND MITOGEN RESPONSE OF LYMPHOCYTES OF ACUTE NONLYMPHOCYTIC LEUKEMIA.

Shiraishi Y, Taguchi H, Niiya K, Shiomi F, Kikukawa K, Kubonishi S, Ohmura T, Hamawaki M, Ueda N
Lab. Clinical Cytogenetics, Dept. Anatomy, Kochi Medical Sch., Nankoku-City, 7-1-51, Kochi, Japan
Cancer Genet Cytogenet; 5(1):1-24 1982

Chromsomes of bone marrow from 28 patients with acute nonlymphocytic leukemia (ANLL) (26 with AML, 2 with AMMoL), 19 of whom had chromosome abnormalities, were studied; 11 cases exhibited previously unreported karyotypic abnormalities. The marrows of two cases had 8-21 translocations associated with an iso-X chromosome in the female patient and with 9q13-and a missing Y in the male patient. Usually, AML patients with an 8-21 translocation have been considered to have a good prognosis; however, our cases had rather short survival times. Therefore, the prognosis of AML with an 8-21 translocation but associated with other abnormalities is still not clear. Centromere spreading (CS), which was originally reported in marrow cells of megaloblastic anemia (B12 and folic acid deficiency), was detected in leukemic cells, disappeared during remission, and reappeared on relapse. These findings suggest that CS may be a new type of abnormality in AML. In two patients with atypical hypoplastic anemia and hemolytic anemia, chromosome abnormalities were detected at the anemic stage. One case with CS was associated with atypical hypoplastic anemia and developed AML after 1 yr; the other with 48,XY,+i(1q),+3,+12 and-14 had hemolytic anemia and developed AMMoL 3 wk later. Interestingly, identical clones were detected both before and after the clinical diagnosis of leukemia. These cases strongly support the concept that some chromosome abnormalities precede the clinical manifestations of leukemia. The present study also revealed that lymphocytes in ANLL respond poorly to PHA in the presence of high numbers of blasts but do respond well to mitogens during remission. Therefore, the response of lymphocytes to PHA may serve as one criterion for determining remission. (Author abstract) (15 Refs)

5. CHROMOSOME ANALYSES IN MULTIPLE MYELOMA.

Balogh E, Kaszas I, Krizsa F, Fleischmann T
II. Belgyogyaszati Osztaly, Szegedi Orvostudomanyi Egyetem, Szeged, Hungary
Orv Hetil; 123(1):35-37 1982

Chromosome analyses were performed in bone marrow cells from 10 patients (4 men and 6 women, 35-75 yr old) with multiple myeloma (MM). Four of the 10 patients had been pretreated; their treatment had consisted of chemotherapy. The type of the serum paraprotein was IgG-kappa in six patients, IgG-lambda in three and IgA-lambda in one. Bence-Jones proteinuria was seen in 4/10 patients. The skeletal system was affected with certainty in five patients, probably in one. The bone marrow was involved in all 10 patients. The chromosome count of the main cell line was 46 in nine patients, 47 in one. Clonal aberrations (+17,-18; 14 micron+, M,-19, +20, and 17p+) were found in five patients. Random anomalies were seen in six patients. The random anomalies were mostly numerical changes in the karyotypes. (15 Refs) (In HUN)

6. DIAGNOSIS OF PLEURAL EFFUSIONS BY CHROMOSOME ANALYSIS.

Falor WH, Ward RM, Brezler MR
75 Arch St., Akron, OH, 44304
Chest; 81(2):193-197 1982

The comparative diagnosis of pleural effusions by chromosome and cytologic analyses was studied in 60 patients. Thirty-three effusions were related to a malignant tumor and 27 were secondary to non-neoplastic disease of the lung, heart, or liver. Chromosome analysis achieved 91% positive diagnoses and cytologic examination 64%. Combination of the two techniques did not increase the number of positive diagnoses. (16 Refs)

7. REGRESSING ATYPICAL HISTIOCYTOSIS: A CUTANEOUS PROLIFERATION OF ATYPICAL NEOPLASTIC HISTIOCYTES WITH UNEXPECTEDLY INDOLENT BIOLOGIC BEHAVIOR.

Flynn KJ, Dehner LP, Gajl-Peczalska KJ, Dahl MV, Ramsay N, Wang N
Dept. Dermatology, Univ. Hosp., Box 98, 420 Delaware St., SE, Minneapolis, MN, 55455
Cancer; 49(5):959-970 1982

Regressing atypical histiocytosis (RAH) of skin is a cutaneous noduloulcerative proliferation of atypical neoplastic histiocytes with concomitant polymorphous inflammation, frequently pronounced epidermal hyperplasia, and an unexpectedly indolent biologic course. Spontaneous regression and recurrence without systemic spread were the course in follow-up periods of over 6 yr. Histopathologically, characteristic-appearing atypical mononuclear and multinucleated 'RAH' cells sho wed erythrophagocytosis as well as ultrastructural, surface marker, and enzyme cytochemical features indicating histiocytic differentiation. Cytogenetic analysis showed aneuploidy and several marker chromosomes including 14q+. Its benign biologic course clearly distinguished this entity from malignant histiocytosis, large cell lymphoma, and Hodgkin's disease. The histiocytic atypical cells further distinguished it from the T-cell lesions of the skin, such as mycosis fungoides and lymphomatoid papulosis. This entity is readily confused with malignant lymphoreticular disease, melanoma, or squamous carcinoma. (Author abstract) (68 Refs)

8. CYTOGENETIC STUDIES IN PATIENTS PREVIOUSLY TREATED FOR HODGKIN'S DISEASE.

Lawler SD, Summersgill BM, McElwain TJ
Royal Marsden Hosp., Fulham Road, London, SW3 6JJ, England
Cancer Genet Cytogenet; 5(1):25-35 1982

A cytogenetic study was made of bone marrow cells and lymphocytes from patients who had been successfully treated with various regimens for Hodgkin's disease. Most of the patients had been off treatment for at least 3 yr before the study began. They were divided into three groups according to the intensity of the therapy received. The frequency of gaps and breaks in the chromosomes of lymphocytes was above normal limits and similar in the three treatment groups. In contrast, the frequency of both lymphocytes and bone marrow cells with rearranged karyotypes was correlated with the intensity of treatment. Clones of cells with an abnormal karyotype were found in only two patients, both of whom were in the group receiving the most intensive therapy, ie, chemotherapy and total nodal irradiation. (Author abstract) (15 Refs)

9. THE 5Q-MINUS SYNDROME - A CHROMOSOMAL ABERRATION WITH CHARACTERISTIC HEMATOLOGICAL PICTURES: PRELEUKEMIA?.

Mueller RA, Auf der Maur P, Beck EA, Deubelbeiss K, Bucher U
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Schweiz Med Wochenschr; 112(7):242-252 1982

The case of a 74-yr-old woman with macrocytic, refractory anemia, typical changes in the bone marrow and a 5q-chromosome in bone marrow cells is presented and the literature of this newly described hematological disorder is reviewed. The syndrome is characterized by partial deletion of the long arms of a chromosome No 5 in bone marrow cells. The chromosomal anomaly is acquired and originates most probably from a pluripotent hematologic stem cell. Hematologic changes are (1) macrocytic, refractory anemia, (2) low to normal leukocyte counts, (3) normal to increased platelet number with marked anisocytosis and a high proportion of megathrombocytes, (4) normal to hypoplastic erythropoiesis and generally small megakaryocytes with nonlobulated nuclei in the bone marrow. In most of the reported cases (16 out of 19) with isolated 5q-anomaly, the clinical picture and laboratory findings remained stationary during a follow-up period of up to 6 yr. In only 2 out of 19 cases did acute leukemia develop. In the presence of additional chromosomal abnormalities, all the cases developed acute leukemia and especially acute myelogenous leukemia. The diagnosis of 5q-syndrome in patients with refractory anemia is of prognostic significance, since it renders possible early recognition of a potentially malignant disorder and early detection of leukemic transformation. (Author abstract) (53 Refs) (In GER)

10. 5Q- SYNDROME IN A PATIENT WITH CHRONIC EXPOSURE TO IONIZING RADIATION.

Mecucci C, Donti E, Bocchini V, Tabilio A, Martelli MF
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Cancer Genet Cytogenet; 5(1):75-80 1982

A report is presented on an interstitial deletion of the long arm of chromosome number 5(5q-), associated with refractory anemia in a patient who had been exposed to chronic ionizing radiation. Six yr of follow-up did not disclose any evolution toward leukemia. (Author abstract) (22 Refs)

DNA CONTENT AND PLOIDY CHANGES ASSOCIATED WITH CANCER

11. QUANTITATIVE HISTOCHEMISTRY OF DNA AND OXYDOREDUCTASES IN THE COMPARATIVE ANALYSIS OF LUNG, STOMACH, AND BREAST CANCERS.

Serov VV, Zolotarevskii VB, Kogan EA, Krysteva-Sedmakova LT, Kudriavtsev IuV, Sklianskaia OA
I. M. Sechenov First Medical Inst., Moscow, USSR
Vestn Akad Med Nauk SSSR; (12):39-49 1981

The results of histochemical determination of DNA content and activities of oxydoreductases (OR) in 32 specimens of lung cancer (LC), 30 specimens of stomach cancer (SC), and 41 specimens of breast cancer (BC) are reported. LC had histology of squamous cell carcinoma, adenocarcinoma, and nondifferentiated (small cell and large cell) carcinoma. BC had histology of intraductal and infiltrative carcinoma. SC had histology of adenocarcinoma, solid carcinoma, and nondifferentiated carcinoma. The decrease of the degree of the differentiation was associated with the increase of the frequency of polyploid cell and DNA content, increase of the role of pentosephosphates pathway in the energy metabolism, increase of the role of glycolysis, and increase of the role of anabolic processes. Tumors with similar histology but different localization differed with respect to the majority of OR. These findings indicate that OR activities and DNA content can be used for differential diagnosis of tumors of different localizations. (48 Refs) (In RUS)

12. SENSITIVE THREE-PARAMETER FLOW-CYTOMETRIC DETECTION OF ABNORMAL CELLS IN HUMAN CERVICAL CANCERS: A PILOT STUDY.

Valet G, Ormerod MG, Warnecke HH, Benker G, Ruhenstroth-Bauer G
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J Cancer Res Clin Oncol; 102(2):177-184 1981

The cell vol, the DNA, and the carcino-embryonic (CEA) or epithelial-membrane (EMA) antigen of formaldehyde-fixed human cervical cells from 21 malignant cervix tumors and 11 normal patients were measured simultaneously with a Fluvo-Metricell flow cytometer. The simultaneous cell vol and DNA measurement provided the distinction of morphologically intact cells from cell debris, the determination of the cell cycle phase combined with the detection of aneuploid cells, and the distinction of inflammatory cells from parenchymal and tumor cells. Malignant samples were recognized because they contained more than 0.5% CEA positive cells which were of intermediate size. CEA and EMA expression in the malignant samples was not linked. The false positive rate in a total of 32 samples was 6.3% when the sum of CEA and EMA positive cells of each cell sample was calculated. No false negative malignant sample was observed. (Author abstract) (26 Refs)

13. DNA PATTERN AND CYTOLOGICAL FINDINGS IN FINE-NEEDLE ASPIRATES OF UNTREATED PROSTATIC TUMORS. A FLOW-CYTOFLUOROMETRIC STUDY.

Ronstrom L, Tribukait B, Esposti PL
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Prostate; 2(1):79-88 1981

Flow-cytofluorometric analysis was used to determine DNA distribution patterns in 500 patients (50-92 yr old; mean age 71 yr) with clinical suspicion of carcinoma of the prostate. Fluorescence of each cell, proportional to nuclear DNA content, was measured at a rate of up to 1,000 cells/sec. Diploid or nondiploid (tetraploid or non-tetraploid) cell populations were identified. Of 301 benign lesions, 278 were diploid, 22 tetraploid, and 1 non-tetraploid. Of 33 suspected carcinomas, 24 were diploid, 6 tetraploid, and 3 non-tetraploid. Of 166 carcinomas, 45 were diploid, 75 tetraploid, and 46 non-tetraploid. Of the 41 well-differentiated carcinomas, 23 were diploid, 17 tetraploid, and 1 non-tetraploid; these values were 21, 52, and 22 for 95 moderateley differentiated carcinomas, and 1, 6, and 23 for 30 poorly differentiated carcinomas, respectively. Thus, differences in nuclear DNA content were observed in morphologically indistinguishable tumors allowing a further subdivision and characterization. Clinical follow-up of patients is necessary to determine the biological significance of these findings. (28 Refs)

14. THE EFFECT OF PLOIDY AND COLCEMID ON THE FREQUENCY OF SPONTANEOUS TRANSFORMATION OF CULTURED CELLS.

Saggioro D, Szpirer J, Scpirer C
Laboratoire de Genetique, Universite Libre de Bruxelles, rue des Chevaux 67, B1640 Rhode-St-Genese, Belgium
Cell Biol Int Rep; 6(1):29-38 1982

Acquisition of the ability of rat fibroblasts of recently established lines possessing pseudodiploid or pseudotetraploid numbers of chromosomes to proliferate in soft agar was investigated. This early transformation-related step occurred at a frequency that was independent of cell ploidy. The main cause of this alteration thus seems not to be the acquisition of recessive mutations. (54 Refs)

15. VARIATIONS OF THYMIDINE KINASE ACTIVITY AND DNA CONTENT IN EHRLICH AND L1210 ASCITES TUMOR CELLS DURING TUMOR GROWTH.

Szikla K, Pokorny E, Hullan L, Holczinger L
Natl. Oncological Inst., Res. Inst. Oncopathology, Budapest, Hungary
Cancer Biochem Biophys; 5(4):259-264 1981

Ehrlich ascites tumor is ip transplanted into Swiss H-riop outbred, and L1210 ascites tumor into BDF1 mice, at rates of approx 10(7) and 10(6) tumor cells per animal, respectively. Animals were sacrificed daily; ascites cells were counted, thymidine kinase (TK) activities of tumor-cell supernatants were determined by 14C-thymidine assay; and DNA content of tumor cells was determined by Feulgen cytophotometry. The growth curve of Ehrlich ascites tumor had four phases, of which the first was a logarithmic one of 4-5 days duration. The L1210 leukemia grew in a two-phase pattern, a 4 to 5-day logarithmic phase being followed by a plateau phase lasting until all animals had died. In Ehrlich ascites tumor growth TK acuvities were high in the first phase and rose again in the 10 to 11-day period. L1210 leukemia progression exhibited only the initial peak in TK activity, and TK activity of L1210 was always lower than that of Ehrlich ascites tumor cytosol. DNA content tended to increase in the Ehrlich ascites tumor cells during development, and shifted from mainly diploid to mainly tetraploid toward the animals death. The av DNA content of L1210 tumor cells was steady over the first 5 days, then declined; DNA distribution shifted toward diploid dominance near the 8th day of the experiment. (26 Refs)

CHROMOSOMAL FRAGILITY AND GENETIC FACTORS PREDISPOSING TO HUMAN CANCER

16. FAMILIAL RESPIRATORY TRACT CANCER. OPPORTUNITIES FOR RESEARCH AND PREVENTION.

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JAMA; 247(7):1020-1023 1982

Case studies of two families with lung and other respiratory tract cancers were investigated. Consenting family members underwent comprehensive evaluation, including physical examination, routine laboratory studies, pulmonary function testing, sputum cytology analysis, and lymphocyte karyotyping. In both families, the environmental influence of smoking and, to a lesser extent, occupational exposures were evident risks. Both families had members with multiple primary malignant neoplasms and probably radiogenic cancers, suggestive of inherent predisposition to environmentally induced neoplasia. Furthermore, one family had a newly recognized syndrome of limb and dental anomalies, and, independently, two members were carriers of a balanced translocation between chromosomes 13 and 14. Efforts were made to prevent further respiratory cancer deaths, to search for laboratory markers of risk, and to store blood and tissue specimens for assays in development. (Author abstract) (21 Refs)

17. DECREASED RATE OF BENZO(A)PYRENE-INDUCED SISTER CHROMATID EXCHANGE IN FIBROBLAST CULTURES FROM PATIENTS WITH LUNG CANCER.

Rudiger HW, Harder W, Maack P, Kohl FV, Schmidt-Preuss U
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J Cancer Res Clin Oncol; 102(2):169-175 1981

Fibroblast cultures from 29 lung cancer patients including 9 familial cases and from 25 healthy controls were investigated. We studied the benzpyrene-induced sister chromatid exchange (SCE) following incubation in the presence of 150 nM benzo(a)pyrene and found spontaneously increased SCE values in the patients' cells but a reduced response to benzpyrene as compared to the control cultures. The benzpyrene-induced SCE was positively correlated with both benzpyrene metabolism and DNA adducts in normal control cells but not in the patients' cells. The ratio of benzpyrene DNA adducts and benzpyrene-induced rate of SCE calculated for the individual cell strains exhibited a bimodal distribution with patients' cells, but not with control cells. We speculate that the described differences between patients' and control fibroblasts might reflect a genetic predisposition to the development of lung cancer in about one half of the patients tested. (Author abstract) (10 Refs)

18. FAMILIAL ERYTHROLEUKEMIA: FOUR CASES OF THE DI GUGLIELMO SYNDROME IN CLOSE RELATIVES.

Nissenblatt MJ, Bias W, Borgaonkar D, Dixon S, Cody RP
7 Wirt St., New Brunswick, NJ, 08901
Johns Hopkins Med J; 150(1):1-9 1982

Erythroleukemia was diagnosed in three brothers during a 6-mo period in 1976. A son of one leukemic had died 5 yr earlier with erythroleukemia. First-degree relatives of these men were evaluated in an attempt to identify contributing factors. Twenty-four relatives have been studied. Immunoglobulin M was elevated in 14 of 16 persons (mean, 352.8 mg/dl; normal, less than 145 mg/dl; p less than 0.001). This was neither a monoclonal protein nor rheumatoid factor. Age-dependent red cell enzymes were increased. Erythrocyte hexokinase was markedly increased in 23 of 24 persons (mean, 35.05 units/100 ml RBC; normal, less than 18 units; p less than 0.001). Evidence for a hemolytic state was absent. Bone marrow samples in eight first-degree relatives were normal. Cytogenetics were normal in 18 relatives. One leukemic exhibited hypoploidy and a marker chromosome. The association of an immunoglobulin abnormality and enzymopathy in the leukemics and relatives alike suggests a hereditary susceptibility to the develo pment of erythroleukemia. The exact link is not identified. (Author abstract) (35 Refs)

19. KLINEFELTER'S SYNDROME AND ACUTE NON-LYMPHOCYTIC LEUKEMIA.

Muts-Homsma SJ, Muller HP, Geraedst JP
Dept. Medicine, Div. Haematology, Univ. Hosp., NL-2333 AA Leiden, The Netherlands
Blut; 44(1):15-20 1982

Case reports are presented of five patients (30-64 yr old) with Klinefelter's syndrome (KS) among 51 male adult patients with acute non-lymphocytic leukemia (ANLL). Peripheral blood was cultured for 24 hr without stimulation and for 72 hr in the presence of phytohemagglutinin (PHA). All chromosome analyses were performed after G-banding. All of the patients had a 47,XXY karyotype; one patient showed the same karyotype when bone marrow cells were cultivated with or without PHA stimulation. Cultures of one patient showed three different cell lines, two of which contained acquired chromosome anomalies, +8 and 20 q-,+21. The incidence of KS in this series (1:10) was much higher than that in the combined data of six newborn studies with 35 cases of the KS chromosome abnormality among 37,779 males (about 1:1,000). It is concluded the Klinefelter's syndrome probably predisposes to the development of ANLL, although the causative factor(s) are unknown. (23 Refs)

20. ACUTE MEGAKARYOBLASTIC LEUKAEMIA ASSOCIATED WITH INTRINSIC PLATELET DYSFUNCTION AND CONSTITUTIONAL RING 21 CHROMOSOME IN A YOUNG BOY.

Pui CH, Williams DL, Scarborough V, Jackson CW, Price R, Murphy S
Div. Hematology-Oncology, St. Jude Children's Res. Hosp., 332 North Lauderdale, P.O. Box 318, Memphis, TN, 38101
Br J Haematol; 50(2):191-200 1982

A 3-yr-old boy with pancytopenia and a paucity of circulating blast cells was found to have acute megakaryoblastic leukemia. Histopathologic investigation of the bone marrow biopsy disclosed replacement by megakaryoblasts and mild-to-moderate reticulin fibrosis. The megakaryocytic origin of these cells was confirmed by their staining properties and by cross-reactivity with rabbit anti-rat platelet serum. Treatment with adriamycin and cytosine arabinoside induced a complete remission of this otherwise rapidly fatal disease. Before chemotherapy, the patient's platelets showed decreased aggregation in response to thrombin and adenosine diphosphate, as well as a defective thrombin-induced serotonin release reaction. Neither functional defect resolved after remission induction, indicating that the platelets were intrinsically abnormal. Most striking was the finding of a constitutional chromosomal defect, a ring

No 21 chromosome, in addition to an abnormal malignant stem line. This appears to be the first reported instance of a constitutional r(21) chromosome associated with acute leukemia. (Author abstract) (31 Refs)

21. DYSKERATOSIS CONGENITA: SURVIVAL, SISTER-CHROMATID EXCHANGE AND REPAIR FOLLOWING TREATMENTS WITH CROSSLINKING AGENTS.

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Mutat Res; 103(3-6):327-332 1982

Normal human fibroblasts NHSF 46 and dyskeratosis congenita (DC) strains DC1KO, DC2K0, and DC1JTO were cultured in Eagle's essential minimal medium, and the lethal effects of the cross-linking agents mitomycin C (MC:0.1-0.5 mg/ml) and 4,5',8-trimethylpsoralen (TMP:10 7-6 1 M) + near-UV light were determined. All DC-strain cells exhibited the same resistance to killing as normal cells for both treatments. Linear SCE induction coefficients were the same after treatment of the four cell lines with both agents, and a baseline SCE frequency of about 5/cell was observed for all strains used. DNA repair processes in DC1K0 cells and NHSF46 cells were shown to be similar by sedimentation velocity analysis. These results may be used to differentiate DC cells from those of Fanconi's anemia, a condition sometimes confused with DC, but in which chromosomes are typically unstable. (16 Refs)

22. INFLUENCE OF ATAXIA TELANGIECTASIA GENE DOSAGE ON BLEOMYCIN-INDUCED CHROMOSOME BREAKAGE AND INHIBITION OF REPLICATION IN HUMAN LYMPHOBLASTOID CELL LINES.

Kohn PH, Kraemer KH, Buchanan JK
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Exp Cell Res; 137(2):387-395 1982

Long-term lymphoblastoid cell lines, obtained by E-B virus transformation of peripheral blood lymphocytes, retain many of the features of hypersensitivity to environmental agents found in primary cultures and fibroblast strains from patients with genetic diseases. Primary lymphocyte cultures from patients with ataxia telangiectasia, a cancer-prone genetic disease, have increased sensitivity to chromosomal damage induced by the radio-mimetic drug, bleomycin. In order to study the expression of ataxia telangiectasia gene dosage in lymphoblastoid cell lines, we examined chromosomal aberrations in lines containing two, one, or no alleles for ataxia telangiectasia obligate heterozygotes, and from presumably normal donors, respectively. Chromosome preparations were made 46 hr after a 2 hr exposure to bleomycin and scored for chromosome breakage, for the relative rate of cell replication as assessed by sister chromatid differentiation patterns, and for the frequency of sister chromatid exchanges. Baseline frequencies of chromosome breakage and sister chromatid exchanges, and baseline rates of cell replication were similar in all nine lymphoblastoid cell lines. Following treatment with 25 or 250 mU/ml bleomycin, all the lymphoblastoid cell lines showed increased chromosome breakage and decreased cell replication. The lymphoblastoid cell lines from the ataxia telangiectasia homozygotes had significantly increased chromosome breakage and d ecreased rate of cell replication after either bleomycin dose in comparison with the normal or with the ataxia telangiectasia heterozygous lines. Sister chromatid exchange frequencies were not altered by bleomycin exposure. (Author abstract) (31 Refs)

23. DNA REPAIR IN NORMAL HUMAN AND XERODERMA PIGMENTOSUM GROUP A FIBROBLASTS FOLLOWING TREATMENT WITH VARIOUS METHANESULFONATES AND THE DEMONSTRATION OF A LONG-PATCH (U.V.-LIKE) REPAIR COMPONENT.

Snyder RD, Regan JD
Univ. Tennessee, Oak Ridge, TN, 37830
Carcinogenesis; 3(1):7-14 1982

Excision repair of DNA in normal and xeroderma pigmentosum complementation Group A fibroblasts was examined following treatment with methyl-methanesulfonate, ethyl-methanesulfonate and isopropyl methanesulfonate. Studies utilizing repair synthesis methods and inhibition with arabinofuranosyl cytosine revealed two distinct phases of repair; one commencing and terminating within the first 3-5 hr after the treatment, and a second, much longer phase extending from 9-35 hr post-treatment. Both phases of repair having a long-patch (uv-like) component, which establishes for the first time the existence of this mode of repair in response to alkane sulfonate damage. While xeroderma cells display somewhat fewer alkaline labile sites in their DNA following alkylation treatment than do their normal counterparts (consistent with earlier observations suggesting a deficiency in a glycosylase or apurinic endonuclease), we are unable to demonstrate a deficiency of these cells in either of the two phases of repair. (Author abstract) (61 Refs)

24. REJOINING OF DNA DOUBLE-STRAND BREAKS IN HUMAN FIBROBLASTS AND ITS IMPAIRMENT IN ONE ATAXIA TELANGIECTASIA AND TWO FANCONI STRAINS.

Coquerelle TM, Weibezahn KF
Kernforschungszentrum Karlsruhe, Institut fur Genetik und fur Toxikologie von Spaltstoffen, Postfach 3640, D-7500 Karlsruhe 1, W. Germany
J Supramol Struct Cell Biochem; 17(4):369-376 1981

Repair of DNA double-strand breaks (DSB) in fibroblasts from normal individuals and patients with ataxia telangiectasia (AT) or Fanconi's anemia (FA) was studied. Cell strains tested included 'Munich' from a normal child, 'Berlin' from a normal adult, AT2BE, AT3BI, and AT5BI from patients with AT, and FA CRL 1196, FA Buse, FA 1424, and FA 3557 from patients with FA. Cell cultures were exposed to gamma-radiation (33 Gray/min for 1.5 min) and incubated at 37 C under aerobic conditions; cells not incubated were irradiated at 0 C. DNA DSB were analyzed by neutral filter elution. The lowest dose of radiation producing measurable DSB was 5 Gray, which produced one DSB/3.2 daltons DNA. At 37 C fibroblasts from normal individuals (adult and child) repaired approx 50% of DSB resulting from 50 Gray within 3 min; after 30 min 90% of DSB were repaired. DSB were repaired by a fast repair mechanism and a slow mechanism. Cells from strain AT2BE showed defective fast and slow repair mechanisms. After long incubation times AT2BE cells retained 4-6% more DSB than normal cells. AT3BI and AT5BI cells showed normal repair mechanisms. FA3557 and FA1424 showed defective fast and slow repair mechanisms. FA CRL 1196 and FA Buse showed normal repair mechanisms. Defective DSB repair is apparently the result of deficient enzyme activity. (20 Refs)

CHROMOSOMES OF HUMAN CELL LINES AND TUMORS IN VITRO

25. HIGH-RESOLUTION ANALYSIS OF CHROMOSOME MARKERS IN BURKITT LYMPHOMA CELL LINES.

Zhang S, Zech L, Klein G
Dept. Medical Cell Genetics, Medical Nobel Inst. Karolinska Institutet, S-104 01 Stockholm, Sweden
Int J Cancer; 29(2):153-157 1982

Using a high-resolution chromosome banding technique, which provided more elongated and distinctly banded chromosomes, some new evidence was obtained for localization of break points in Burkitt lymphoma marker chromsomes. As a result, the characteristic translocation between chromosomes 8 and 14 was designated as t(8;14) (q24.1;q32.5) and the deletion of chromosome 15 was designated as del(15) (q13q15). (Author abstract) (19 Refs)

26. HUMAN PANCREATIC ADENOCARCINOMA LINE CAPAN-1 IN TISSUE CULTURE AND THE NUDE MOUSE. MORPHOLOGIC, BIOLOGIC, AND BIOCHEMICAL CHARACTERISTICS.

Kyriazis AP, Kyriazis A, Scarpelli DG, Fogh J, Rao MS, Lepera R
Dept. Pathology, Univ. Cincinnati, 231 Bethesda Ave., Cincinnati, OH, 45267
Am J Pathol; 106(2):250-260 1982

Human pancreatic ductal adenocarcinoma line Capan-1 was studied in tissue culture and the nude mouse. In tissue culture, the neoplastic cells grew as large epithelial-like mucin-producing cells. Sc and ip transplantation of neoplastic cells into nude mice resulted in tumor formation characterized by marked invasiveness and distant metastases. Histologically, the tumor appeared as a well-differentiated mucin-producing adenocarcinoma morphologically resembling the tumor of origin. Chromosomal analysis showed a human karyotype with a chromosome number between 51-61. Lactate dehydrogenase and beta2-microglobulin used as tumor markers were present in both tissue culture and the serum of tumor-bearing mice. The neoplasm, which was characterized by an increased level of cAMP, had lost completely the ability to respond to secretin stimulation. The tumor grown in the nude mouse was resistant to treatment with 5-fluorouracil, behavior identical to that of the original tumor. Diphtheria toxin resulted in complete tumor destruction. Because Capan-1 tumor grown in the nude mouse shows morphologic, biologic, and biochemical characteristics similar to the tumor of origin, it may be an invaluable tool in furthering understanding of the biology of human pancreatic cancer. (Author abstract) (41 Refs)

27. A NEW HUMAN CELL LINE DERIVED FROM A POORLY DIFFERENTIATED ENDOMETRIAL ADENOCARCINOMA.

Gal D, Forney JP, Dev VG, Porter JC
Dept. Obstetrics and Gynecology, Univ. Texas Health Science Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX, 75235
Gynecol Oncol; 13(1):50-57 1982

Establishment and characterization of an endometrial adenocarcinoma cell line are described. The tumor cells, designated AC-258, originated from a patient with a poorly differentiated adenocarcinoma of the endometrium. These cells have been passed in culture more than 102 times and have maintained their morphological and chromosomal integrity in a fashion suggestive of monocloning. Cells from passages 1, 58, and 102 were aneuploid. The av number of chromosomes per cell was 64.8, and 8-17 marker chromosomes per cell were identified and described. Histological evaluation of tumor explants from three passages grown in nude (athymic) mice revealed morphologic identity. The doubling time of AC-258 was 22 hr. No detectable estrogen- or progesterone-binding proteins were found. The AC-258 cell line provides researchers with another tool with which to investigate biochemical and biological properties of human cancer cells. (Author abstract) (12 Refs)

CHROMOSOMES OF ANIMAL CELL LINES AND TUMORS

28. CHROMOSOME ALTERATION AND DEVELOPMENT OF TUMORS. XXIV; HYPO-PENTAPLOID CHROMOSOME CONSTITUTION OF A SPONTANEOUS TUMOR DEVELOPMENT IN THE OCEANIAN TYPE BLACK RAT, WITH PARTICULAR REFERENCE TO CENTROMERIC FISSION.

Yosida TH
National Inst. Genetics, Misima, Japan
Proc Jpn Acad [B]; 57(7):260-265 1981

Detailed chromosomal study of a spontaneously developed hypo-pentaploid (HPP) tumor in a male Oceanian type black rat (Rattus rattus rattus) was performed focusing on the relation between the karyotype (KT) alteration and the tumor development. Fibrosarcoma developed in the dorsal side near the right thigh. Normal KT was observed in the tail culture method; 38 chromosomes (CR) in 50 analyzed cells. Distribution of CR numbers in 50 tumor cells ranged from 38-150. Cells with 91-95 CR occurred most frequently (60%), 12% were cells with hypo-tetraploid constitution (71-75 CR), and 6-2% other CR. The tumor is characterized by HPP type. Total CR numbers, CR pair 1, and metacentric autosome pairs M1 and M2 are presented. Numbers of pair 1, M1, and M2 were not always constant. The ploidy of CR differs according to the CR pair. The centromeric fission was often in the large M2 CR. M1 metacentric CR were always stable. According to polyploidization, half the number of M2 elements dealt with centromeric fission. The CR constitution consist of elements such as hexasomic, pentasomic, tetrasomic, trisomic, and disomic, indicating that the tetraploidization may first occur following octoploidization as a result of the sequential duplication. An unequal distribution of CR due to non-disjunction or abnormal separation may cause the establishment of the tumor with a HPP stem line. (6 Refs)

29. VARIANTS OF THE RAT BASOPHILIC LEUKEMIA CELL LINE FOR THE STUDY OF HISTAMINE RELEASE.

Siraganian RP, McGivney A, Barsumian EL, Crews FT, Hirata F, Axelrod J
Lab. Microbiology and Immunology, Natl. Inst. Dental Res., Bethesda, MD, 20205
Fed Proc; 41(1):30-34 1982

Cloning of the rat basophilic leukemia (RBL) cell lines demonstrates variability in cell chromosome number (approx 44-70) and in their capacity to release histamine following an IgE- or Ca++-ionophore stimulus. After IgE activation there is increased phospholipid methylation, Ca++ influx, arachidonic acid, and histamine release. On Ca++-ionophore A23187 stimulation, phospholipid methylation is not increased, but Ca++

influx, arachidonic acid, and histamine release occur. Variants of the RBL-cloned sublines defective at different stages in the release process were obtained and used to sequence the different events in the release process: IgE activation is followed by methylation, Ca++ influx, arachidonic acid, and histamine release. However, there are other variants with defects in intermediate steps in the pathway, eg, increased phospholipid methylation that is not followed by Ca++ influx or arachidonic acid release not followed by histamine release. Isolating variants carrying drug-resistance markers made hybridization (reconstitution) experiments possible. Two variants were recognized, each of which was deficient in one of the two phospholipid methyltransferase enzymes. Neither of these two variants released histamine; hybrids formed by fusion of these two cell lines have both phospholipid methyltransferase enzymes and release histamine. By other complementation experiments, groups of variants with defects at different steps in the histamine release sequence were recognized. Clearly, these basophilic leukemia cell lines provide a unique system for the study of the mechanism of histamine release. (Author abstract) (25 Refs)

30. ISOLATION AND PROPERTIES OF CHINESE HAMSTER LUNG CELLS RESISTANT TO ELLIPTICINE DERIVATIVES.

Salles B, Charcosset JY, Jacquemin-Sablon A
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Cancer Treat Rep; 66(2):327-338 1982

Chinese hamster lung cells resistant to 9-OH-ellipticine (9-OH-E) were selected in vitro by adding stepwise increasing drug concentrations to the cell growth medium. This selection procedure resulted in the isolation of two sublines, about 10-fold and 12-fold resistant to 9-OH-E. This level of resistance did not increase even after about 30 months of drug exposure. Cytogenetic studies revealed that the resistant cells carry several discrete karyotype modifications, the most striking being the absence of one No. 5 chromosome and the presence of a marker chromosome characterized by peculiar G-banding. Development of 9-OH-E resistance was also associated with some changes in cell properties such as modifications of morphology and growth parameters, lower oncogenic potential, and cross-resistance to a variety of antitumor agents. Although these results suggest that the resistance is associated with a modification of cell membrane properties, drug uptake studies did not show any significant difference between the parental sensitive cells and the resistant sublines. (Author abstract) (36 Refs)

31. VARIATIONS IN CHROMOSOME NUMBERS AND THEIR POSSIBLE RELATIONSHIP TO THE DEVELOPMENT OF 8-AZAGUANINE RESISTANCE IN V79 CHINESE HAMSTER CELLS.

Fox M, Radacic M
Paterson Lab., Christie Hosp. and Holt Radium Inst., Withington, Manchester M2O 9BX, England
Cell Biol Int Rep; 6(1):39-48 1982

Evidence is presented for breakdown of heteroploid V-79 cells both during growth in 8-azaguanine and after removal of cells from selective pressure. Results suggest that acquired during effects at autosomal loci controlling either catabolic enzymes of the purine synthetic pathway or a dominant suppressor of hypoxanthine-guanine-phosphoribosyl-transferase activity. (18 Refs)

32. THE MECHANISM OF GENETIC RESISTANCE TO MAREK'S DISEASE IN CHICKENS.

Powell PC, Lee LF, Mustill BM, Rennie M
Houghton Poultry Res. Station, Houghton, Huntingdon, Cambridgeshire, PE17 2DA, England
Int J Cancer; 29(2):169-174 1982

Genetic resistance to Marek's disease in RPL line-6 chickens is expressed not only at the level of host immunological responses against virus and tumor antigens, but also at the level of target lymphoid cells for virus infection and transformation. The nature of the target cell involved was investigated. Spleen cells from susceptible line-7 chickens adsorbed more Marek's disease virus and turkey herpesvirus in vitro than line-6 spleen cells. In the case of Marek's disease virus this was reflected in the replicative ability of the virus in vivo. Transplantation of thymus fragments from 1-day-old line-7 chickens into thymectomized line-6 chickens conferred a high degree of susceptibility on the latter, but the transplantation of spleen or bursa fragments had no significant effect. The reverse procedure, ie grafting of line-6 thymi into line-7 chickens, did not diminish the susceptibility of the recipients. In each treatment group the observed titers of leukocyte-associated viremia correlated with the susceptibility of the group to Marek's disease. Histologically the grafted thymus fragments became depleted of lymphocytes immediately after transplantation. By 6 days there was substantial recovery, apparently as a result of repopulation of the thymic epithelium by host stem cells. This was confirmed by transplanting thymus fragments between individuals of opposite sexes. Karyotype analysis showed that the thymus contained lymphocytes of the sex of the recipient. However, karyotype analysis of lymphoma cells taken from recipient line-6 chickens that had received thymus grafts from line-7 birds of the opposite sex showed that, in the majority of cases, the lymphomas consisted of cells of donor origin. It is concluded that the susceptibility of line-7 chickens is largely attributable to the greater susceptibility of their T-lymphocytes to infection and transformation by Marek's disease virus, and that this susceptibility can be transferred to genetically resistant line-6 birds by adoptive transfer of the cells in the form of thymus fragments. (Author abstract) (16 Refs)

GENE MAPPING STUDIES

33. GENETIC MAPPING OF ECOTROPIC MURINE LEUKEMIA VIRUS-INDUCING LOCI IN SIX INBRED STRAINS.

Kozak CA, Rowe WP
Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
J Exp Med; 155(2):524-534 1982

Mendelian segregation analysis was used to map chromosomal genes for the induction of endogenous N- and B-tropic ecotropic retroviruses (V loci) in high and low leukemic mouse strains. Segregation analysis resulted in the genetic mapping of V loci in six inbred strains to five mouse chromosomes. The V locus of A/J was mapped to chromosome 5 and shown to be allelic with that of BALB/cJ and C3H/HeJ (Cv); this suggests that Cv represents a stable ancestral V locus present in Bagg albino stocks before separation of inbred lines. The single, poorly inducible V locus of C57BL/10J and one of the four high virus loci of C58/Lw were mapped to the same region of chromosome 8 and may present an allelic pair with different patterns of expression. An N-tropic V locus of the SEA/GnJ mouse was mapped to chromosome 9, and one of the three V loci of C3H/FgLw was mapped to chromosome 7. The endogenous B-tropic virus of B10.BR/SgLi was mapped to chromosome 11. Several of the endogenous proviral sequences appear to be closely linked with cellular genes involved with sensitivity or resistance to retroviral infection or affecting lymphoid differentiation. Identification and separation of individual V loci aids in their characterization and makes it possible to identify DNA fragments carrying biologically defined proviruses. (26 Refs)

34. CHORIONIC GONADOTROPIN SYNTHESIS AND GENE ASSIGNMENT IN HUMAN:MOUSE HYBRID CELLS.

Kohler PO, Riser M, Hardin J, Boothby M, Boime I, Norris J, Siciliano MJ
Dept. Medicine, Univ. Arkansas, Little Rock, AR
Adv Exp Med Biol; 138:405-418 1982

Chorionic gonadotropin (hCG) was studied using somatic cells as a technique for mapping the structural genes for hCG and human:mouse hybrid cells. Analysis of hybrid clones producing hCG and correlation with the retention of certain human chromosomes permitted localization of the hCG genes. Enzymatic chromosome markers in hybrid clones, percentages of cells retaining each human chromosome by morpho logy, and relationship of hCG synthesis to chromosomes 10 and 18 in subclones of 124c-1 are presented. (32 Refs)

35. REGULATION OF CASEIN GENE EXPRESSION IN HORMONE-DEPENDENT MAMMARY CANCER.

Rosen JM, Supowit SC, Gupta P, Yu LY, Hobbs AA, Dao TL, Topp, Hilf
Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030
Banbury Rep; 8:397-424 1981

Structure, organization, and expression of the casein gene (CG) family and the alpha-lactalbumin gene in the normal mammary gland, and altered regulation of CG expression and gene expression in general in hormone-dependent mammary cancer, were studied. Milk protein structural genes, hormonal regulation of milk protein messenger RNA accumulation in rat mammary gland organ culture, milk gene organization and chromosomal localization, CG expression in hormone-dependent mammary cancer, methylation patterns of the CG, DNA rearrangement in mammary tumors (MT), and expression of unique single-copy DNA sequences in 7,12-dimethylbenz(a)anthracene-induced MT are reviewed. New approaches may help explain the regulation of differentiated function in the normal mammary gland and deviation of the mechanisms in hormone-dependent breast cancer. (38 Refs)

36. CDNA CLONES CODING FOR THE HEAVY CHAIN OF HUMAN HLA-DR ANTIGEN.

Lee JS, Trowsdale J, Bodmer WF
Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Proc Natl Acad Sci USA; 79(2):545-549 1982

Two cDNA clones, pDRH1 and pDRH2, containing sequences specific for human HLA-DR antigens were isolated from a bank of cDNA clones made from partially purified HLA-DR mRNA from the human lymphoblastoid cell line Maja. The clones were specific for the Mr 34,000 HLA-DR antigen glycoprotein chain. The identity of these clones was established by (i) their ability to hybridize specifically to HLA-DR mRNA in a positive selection assay; (ii) mRNA species hybridizing to the cDNA clones were expressed in B-cell but not in T-cell or fibroblast cell cultures; and (iii) a nucleotide sequence in the longer clone, pDRH2, could be translated into an amino acid sequence that is identical to the limited NH2-terminal amino acid sequence available for the purified HLA-DR antigen Mr 34,000 chain. Analysis of dNA from human, mouse, and human-mouse somatic cell hybrid lines by Southern transfer of restriction endonuclease digests indicated that the HLA-DR heavy chain is encoded in chromosome 6. This finding is compatible with the location of at least one of the HLA-D/DR heavy chain genes within the HLA region. In addition, the sequences coding for HLA-DR heavy chain appear to be present in only one or a few copies in the genome and to be relatively simple in structure. (Author abstract) (43 Refs)

37. CORRELATION BETWEEN VARIANT TRANSLOCATION AND EXPRESSION OF IMMUNOGLOBULIN LIGHT CHAINS IN BURKITT'S LYMPHOMAS AND LEUKEMIAS.

Lenoir G, Preud'homme JL, Bernheim A, Berger R
Programme des Mecanismes de la Cancerogenese, Centre international de Recherche sur le Cancer, 150, cours Albert-Thomas, 69372 Lyon Cedex 2, France
C R Acad Sci [III] (Paris); 293(8):427-429 1981

Expression of immunoglobulins (IG) in Burkitt's lymphomas (19 lines) and leukemias (1 line) are discussed in relation to observed chromosome abnormalities. Of the 19 lymphoma lines, 12 were non-endemic and 7 did not contain the Epstein Barr virus. IG light chains produced varied according to the type of translocation. In 17/18 cases with translocation t(8;14), the light chains of surface and cytoplasmic IG were type kappa (9 cases) or type gamma (8 cases). The cells of patient 18 did not express any detectable light chains. In 3/5 cases of translocation t(2;8), the light chains were type kappa with light chain expression in 1/3; the two other cell lines exhibited a pre-B phenotype. Of six cases with translocation t(8;22), IG with gamma chains were found in 5 and a pre-B phenotype in the sixth. IgM, sometimes associated with IgD, was found in 17/19 cell lines; two cell lines were characterized by monoclonal gamma IgG (translocation t(8;14) in one case and t(8;22) in the other). The results indicated the existence of a relationship between translocations t(2;8) and t(8;22) and light chain expression: kappa in the case of t(2;8) and gamma in the case of t(8;22). (12 Refs) (In FRE)

MOLECULAR CYTOGENETICS

38. ANTIBODIES SPECIFIC FOR MITOTIC HUMAN CHROMOSOMES.

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Exp Cell Res; 137(2):381-386 1982

The induction of premature chromosome condensation in an interphase cell immediately following fusion with a mitotic cell suggests the presence of factors in the mitotic cells that are responsible for the transformation of an interphase nucleus into prematurely condensed chromosomes (PCC). Several lines of evidence suggest that these factors are proteins present in the cytoplasm of mitotic cells. The objective of the study was to raise antibodies to the factors responsible for PCC. Cytosol from synchronized mitotic HeLa cells was injected into rabbits in order to obtain antiserum. The IgG fraction from this antiserum reacted with 98% of mitotic HeLa cells when tested by indirect immunofluorescence. Most of the fluorescence was localized on the chromosomes. About 5% of the interphase nuclei also reacted with the antiserum, but 50% of these cells were in early G1. Antigenic reactivity was induced in the condensing interphase chromatin in 31% of the interphase nuclei found in mitotic-interphase fused cells. Rodent cells did not react with the antibody by indirect immunofluorescence. Mitotic HeLa cells were able to induce antigenic reactivity in 23% of interphase Chinese hamster ovary (CHO) cell nuclei in fused binucleate cells, whereas the converse was not true of mitotic CHO cells. Enzyme digestion and incubation with denaturing agents suggested that antigenic reactivity depended on a DNA-non-histone protein complex. (Author abstract) (13 Refs)

39. TRNA PRECURSOR TRANSCRIBED FROM A MUTANT HUMAN GENE INSERTED INTO A SV40 VECTOR IS PROCESSED INCORRECTLY.

Zasloff M, Santos T, Hamer DH
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Nature; 295(5849):533-535 1982

Functional properties of the human variant initiator transfer (t)RNA gene within an intact cell were assayed by studying its transcription from a simian virus 40 (SV40) recombinant during lytic infection of African green monkey kidney cells. Structure of the SV40-tRNAiMet recombinant (SVtm) used contained a 1.15-kilobase fragment of human genomic DNA harboring a single tRNAiMet gene. Resulting viral stocks were used in the study. Total cytoplasmic and nuclear RNA were recovered from the infected cells and analyzed. Cytoplasmic and nuclear fractions from SVtm-infected cells contained a single low-mol wt species approx 89 nucleotides long. The RNA species accumulating in the SVtm infection was analyzed by classical fingerprinting techniques. The transcript was a precursor of the variant tRNAiMet. Only a preliminary analysis of base modification within the precursor was performed. Hybridization of equal amounts of gel-purified tRNA from SVtm and control infections to filter bound tRNAiMet DNA occurred at approx equal rates and reached max level of hybridization of approx 1% of the input radioactivity. Results indicate that conversion of the mutant precursor to mature tRNA does not occur with any significant efficiency, suggesting that mutations within eukaryotic tRNA genes may be more prevalent than assumed from the limited sequence variation observed in mature tRNA species. (22 Refs)

40. MOLONEY MURINE LEUKEMIA VIRUS-INDUCED TUMORS: RECOMBINANT PROVIRUSES IN ACTIVE CHROMATIN REGIONS.

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Nucleic Acids Res; 10(2):577-592 1982

The DNase I sensitivity of chromosomal DNA regions carrying integrated proviral genomes of Moloney (M-MuLV) and AKR Murine Leukemia Virus (AKR-MuLV), and the cellular homologue of the mos-gene (c-mos) of Moloney Sarcoma Virus (MSV) were studied in tumor tissues of leukemic mice. The genetically transmitted sequences of M-MuLV, AKR-MuLV, and the c-mos gene are all in DNase I resistant chromatin conformations in M-MuLV-induced tumors. Each M-MuLV-induced tumor contained at least one somatically acquired in tegrated recombinant MuLV genome that displayed two main characteristic features of active chromatin; (a) a configuration hypersensitive to DNase I, and (b) extensive hypomethylation. DNase I hypersensitive sites were mapped at the junction of cellular sequences and the 5'-viral large terminal repeat (LTR). Expression of a recombinant MuLV seems therefore to be a necessary feature to maintain the transformed state. (Author abstract) (28 Refs)

41. ISOLATION OF TRANSFORMING DNA BY COSMID RESCUE.

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Proc Natl Acad Sci USA; 79(2):520-524 1982

A procedure has been developed to allow the recovery of an integrated plasmid genome from a transformed cell, together with large areas of the flanking DNA sequences. DNA from Saccharomyces cerevisiae BAS2, in which the pBR322-ura 3 plasmid (Ylp5) is integrated at the yeast histone H2A and H2B locus, was used to generate a cosmid library, using a new cosmid vector (pTL5) that is ampicillin sensitive and tetracycline resistant. Colonies were selected for ampicillin resistance, which was conferred by the incorporation of the integrated pBR322 beta-lactamase gene into the recombinant cosmid. Restriction enzyme and blot hybridization analyses show that the rescued clones contain the yeast histone genes in addition to the Ylp5 sequences; a total of approx 50 kilobase pairs of DNA sequences flanking the plasmid was recovered as a series of overlapping cosmids. This approach should allow the recovery of most genes that can be linked to a marker pBR322 sequence and for which a specific phenotype can be selected in a recipient eukaryotic cell. (Author abstract) (15 Refs)

42. INDUCER-RESPONSIVE EXPRESSION OF THE CLONED HUMAN INTERFERON BETA1 GENE INTRODUCED INTO CULTURED MOUSE CELLS.

Ohno S, Taniguchi T

Dept. Biochemistry, Cancer Inst., Japanese Foundation Cancer Res., Tokyo 170, Japan

Nucleic Acids Res; 10(3):967-977 1982

A hybrid plasmid was constructed from pSV2-Egogpt and the cloned 1.8 kilobase chromosomal DNA segment which contains the human interferon (HIFN-beta1) gene and its flanking sequences. Cultured mouse FM3A cells were transfected by the hybrid plasmid and several Ecogpt+ clones were selected. Southern blot analysis of the DNA from these mouse cell clones showed that two of them contained a few copies of the 1.8 kilobase human DNA. Synthesis of mRNA characteristic of the HIFN-beta1 mRNA increased as measured by RNA blot analysis when those clones were treated with Newcastle disease virus or with poly(I):poly(C). In addition, the induced mouse cell clones gave rise to the synthesis of human IFN-beta1. These results suggest the presence of a unique nucleotide sequence in the 1.8 kilobase DNA which is sufficient for the inducer- responsive expression of the human IFN-beta1 gene. (Author abstract) (30 Refs)

43. STRUCTURE OF ADENOVIRUS CHROMATIN.

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Biochim Biophys Acta; 696(1):76-86 1982

The structure of adenovirus Type 2 chromatin isolated from wild-type and ts1 virions was investigated by micrococcal nuclease digestion and electron microscopy. Partial digestion of wild-type and ts1 chromatin with micrococcal nuclease generated a multimeric DNA smear devoid of the 200 basepair nucleosome repeating pattern characteristic of cellular chromatin. However, 11 S monomer cores of 150 basepairs were detectable. The chromatin of ts1 (39 C) was more resistant to digestion by micrococcal nuclease. Two-dimensional electrophoresis of the monomer core showed that wild-type core contained protein VII while ts1 (39 C) core contained PVI and PVII. Protein V appears to be located on the variable-length intermonomer region. Crosslinking studies suggest that proteins PVII and VII exist in dimeric form within the monomer core. Electron microscopy revealed a 5.5-fold-condensed 2-micron-long beaded structure with about 200 monomer particles spaced irregularly. Based on these observations, a model for adenovirus prochromatin and chromatin is proposed that differs in important aspects from the model proposed previously. (Author abstract) (26 Refs)

44. DNA METHYLASE ACTIVITY OF NORMAL LIVER, REGENERATING LIVER, AND A TRANSPLANTABLE HEPATOCELLULAR CARCINOMA.

Walker MS, Becker FF
(c/o Becker) Dept. Pathology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Cancer Biochem Biophys; 5(3):169-173 1981

DNA methylase was obtained from regenerating rat liver (RRL) from male ACI animals in which transplantable hepatocellular carcinoma (THC 252) had been induced by exposure to N-2-acetylaminofluorene, from normal rat livers (NRL), and from THC 252 nuclei (THC). The activities of DNA methylase in crude extracts of NRL, RRL, and THC, determined by methylation of denatured Micrococcus luteus DNA, were as follows: NRL less than RRL less than THC. A similar assay with Escherichia coli and calf thymus DNAs, both single- and double-stranded, confirmed that methylase activities of the three tissues remain in the same order regardless of substrate. Methylation saturation studies performed with DNAs from the same three rat tissues showed that THC 252 DNA is hypomethylated, and that the undermethylation does not result from an inability of THC 252 methylases to methylate THC 252 DNA. The results confirm earlier findings obtained by direct analysis of 5-methylcytosine content; chromatin composition or configuration is the most likely explanation f or hypomethylation. (25 Refs)

45. POLY(ADP-RIBOSE) GLYCOHYDROLASE IS PRESENT IN METAPHASE CHROMOSOMES OF HELA S3 CELLS.

Tanuma S, Arita T, Kawashima K, Endo H
Dept. Physiological Chemistry, Faculty Pharmaceutical, Sciences Teikyo Univ., Sagamiko, Kanagawa 199-01, Japan
Biochem Biophys Res Commun; 104(2):483-490 1981

A chromatin system that detects hydrolytic enzymes present in metaphase chromosomes by measuring acid-insoluble radioactivity liberated from chromosome-bound poly(ADP-ribose) (av chain length 14) was used to confirm the presence of active poly(ADP-ribose) glycohydrolase in metaphase-arrested HeLa S3 cell chromosomes. The optimum conditions for hydrolysis of metaphase chromosome-bound poly(ADP)ribose by the glycohydrolase were similar to those for partially purified enzyme from calf thymus. Treatment of the hydrolytic product with phosphodiesterase or alkaline phosphatase demonstrated that it was entirely ADP-ribose. The enzyme may aid the extension of condensed chromosomes, but its exact role remains to be elucidated. (21 Refs)

46. IN VIVO THIOPHOSPHORYLATION OF CHROMOSOMAL PROTEINS. RECOVERY AND ANALYSIS OF HELA HISTONES AND DERIVATIVE PHOSPHOPEPTIDES.

Sun IY, Allfrey VG
Rockefeller Univ., New York, NY, 10021
J Biol Chem; 257(3):1347-1353 1982

HeLa cells are shown to incorporate [35S]thiophosphate (added to the medium as sodium thiophosphate) into the gamma-positions of ATP and GTP, and into other nucleotides. Under these conditions there is a transfer of radioactive thiophosphoryl groups to histones H1, H2A, H3, and H4. The newly thiophosphorylated chromosomal proteins can be recovered selectively by affinity chromatography on organomercurial-Sepharose columns. The thiophosphorylated histone H1 and its NH2-terminal and COOH-terminal fragments were subjected to tryptic digestion and the sulfur-derivatized phosphopeptides were isolated by Hg-affinity chromatography prior to electrophoretic separation of different sites of modification. Thiophosphate was found to be incorporated into both serine and threonine residues of histone H1 in HeLa cells during logarithmic growth. When [3H]threonine and nonradioactive thiophosphate were employed simultaneously as precursors, the thiophosphorylated H1 molecules retained on the mercury column also showed the presence of the [3H]threonine label. It follows that newly synthesized H1 molecules are subject to thiophosphorylation in the growing cell cultures. (Author abstract) (49 Refs)

47. REARRANGEMENTS OF DNA-PROTEIN INTERACTIONS IN ANIMAL CELLS COUPLED WITH CELLULAR GROWTH-QUIESCENCE TRANSITIONS.

Lichtenstein AV, Sjakste N, Zaboykin MM, Shapot VS
All-Union Oncological Scientific Center, Moscow 115478, USSR
Nucleic Acids Res; 10(3):1127-1145 1982

Overall DNA-protein interactions in animal cells undergo drastic changes coupled with cellular transitions from quiescence to growth and reversely as revealed by nucleoprotein-Celite chromatography. DNA of chromatin was found to exist in one of the two sharply distinct alternative forms, namely, either tightly or weakly bound to protein moiety. These forms are specific for cycling and quiescent cells, respectively. The tight DNA-protein interactions characterize all cycling cells independent of the cell cycle phase. Transition of DNA of cycling cells from one form to another was observed as a result of treatment of isolated nuclei with DNase I. (Author abstract) (18 Refs)

48. EFFECTS ON CHROMOSOMAL PROTEINS IN SISTER CHROMATID DIFFERENTIATION BY INCORPORATION OF 5-BROMODEOXYURIDINE INTO DNA.

Buys CH, Osinga J, Van Der Veen AY
Dept. Human Genetics, State Univ. Groningen, Groningen, The Netherlands
Exp Cell Res; 137(2):452-455 1982

When fixed metaphase chromosomes of human lymphocytes grown in the presence of BrdUr for two cell cycles were stained with amino group-specific 2-methoxy-2,4-diphenyl-3(2H)furanone (MDPF) after a previous extraction of DNA, sister chromatids showed a light-independent differential staining. Although more faintly differential, a similar staining pattern being just the reverse of the DNA-specific DAPI pattern was obtained without prior removal of DNA. We conclude that the chromatid containing bifilarly BrdUr-substituted DNA has a higher protein content, at least after fixation, than the chromatid containing unifilarly BrdUr-substituted DNA. Possibly, a higher degree of BrdUr substitution leads to a tighter binding of chromosomal proteins. In line with this suggestion we found a markable difference in DNA extractability of BrdUr-containing and normal cytological preparations. (Author abstract) (22 Refs)

49. HISTONE H1 SUBFRACTIONS AND H1(0) TURNOVER AT DIFFERENT RATES IN NONDIVIDING CELLS.

Pehrson JR, Cole RD
Dept. Biochemistry, Univ. California, Berkeley, Berkeley, CA, 94720
Biochemistry; 21(3):456-460 1982

When cell division was inhibited in mouse neuroblastoma cells by high cell density or by serum deprivation, levels of histone H1(0) increased by a factor of three. Inhibition of cell division by butyrate increased H1(0) seven-fold. In addition to the increase in H1(0), changes were seen in the proportions of H1 subfractions whenever division was inhibited. These canges were only partly due to phosphorylation. When cell division was very active, a pulse of radioactive lysine labeled the various forms of H1 nearly in proportion to their protein mass. A chase of the radioactivity from such pulse-labeled cells showed a rapid turnover of the subfraction H1c, while the other forms of H1 turned over slowly, like the core histones. The inhibition of cell division reduced lysine incorporation into the subfractions of gel band H1a,b nearly as much as it reduced core histone synthesis, but H1c and H1(0) were not so drastically affected. Relative to incorporation into core histones, incorporation into H1c and H1(0) was 4-fold and 20-fold greater, respectively, in mitotically inactive cells. When this radioactivity was chased with unlabeled lysine, H1(0) was quite stable, but H1c and one of the H1 subfractions of the H1a,b band turned over rapidly. Unequal turnover of H1 subfractions and the difference in behavior between H1(0) and the more common H1's show how the recipe of H1 components can be varied even in the absence of DNA synthesis. These results are consistent with a chromatin repair process and also with a designed modulation of chromatin functions. (Author abstract) (32 Refs)

50. CHARACTERISTICS OF ENZYMATIC DNA METHYLATION IN CULTURED CELLS OF HUMAN AND HAMSTER ORIGIN, AND THE EFFECT OF DNA REPLICATION INHIBITION.

Woodcock DM, Adams JK, Cooper IA
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Biochim Biophys Acta; 696(1):15-22 1982

In mammalian cells, inhibitors of DNA replication have been shown to induce chromosomal aberrations, cell death and changes in gene control. Inhibition of DNA synthesis has been reported to induce hypermethylation of mammalian DNA (enzymatic postsynthetic formation of 5-methylcytosine). These 5-methylcytosines in mammalian DNA have variously been suggested to be important in gene control, DNA repair, and control of DNA replication. In establishing the normal characteristics of enzymatic DNA methylation, we have demonstrated that, in asynchronously growing cells of both human and hamster origin, some cytosine methylation is delayed for several hr after strand synthesis and that this delayed methylation is completed before the DNA strand acts as a template for DNA replication in the next S-phase. Further, in testing whether the deleterious effects on mammalian cells of DNA synthesis inhibitors might be mediated via changes in enzymatic DNA methylation, we have found, contrary to some previous findings, no evidence for any change in the level of DNA methylation in DNA strands synthesized during 6 hr of treatment of cells of human origin with high concentrations of four different inhibitors of DNA replication or during the 4 hr following the 6 hr treatment. Almost totally blocking DNA replication had no effect on the small amount of delayed methylation of DNA strands not involved in semi-conservative replication during the time of the experiment. This lack of effect on DNA methylation was obtained when the labeling medium contained normal, undialyzed serum. In contrast, if dialyzed serum was used in the labeling medium in order to maximize L-[Me-3H]methionine utilization, highly variable, totally irreproducible patterns of apparent DNA hypermethylation were obtained. (Author abstract) (27 Refs)

51. DEGRADATION OF HELA CELL CHROMATIN BY NEOCARZINOSTATIN AND ITS CHROMOPHORE.

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Biochim Biophys Acta; 696(1):7-14 1982

Chromatin is the in vivo target site for neocarzinostatin, a DNA strand scission antitumor drug. The effect of neocarzinostatin and its active chromophore component on HeLa cell chromatin is described here. Chromatin consisting of a mixture of mono-, di-, tri- and larger nucleosome fragments is prepared by micrococcal nuclease digestion of HeLa cell nuclei. Drug-induced conversion of chromatin to smaller sized fragments is measured by electrophoresis of the DNA on non-denaturing 4% polyacrylamide gels. Chromatin breakdown measured under these conditions is double-stranded in nature. In the presence of 2 mM dithiothreitol, neocarzinostatin causes degradation of large chromatin fragments and a loss of distinct nucleosome peaks. Detection of chromatin breakdown by neocarzinostatin is dependent upon the concentration of chromatin in the assay. When chromatin is increased from 14 to 70 ug/ml, changes in the larger fragments caused by 100 ug/ml neocarzinostatin become less obvious and are almost undetectable at 140 ug/ml chromatin. No change is observed when chromatin is treated with either neocarzinostatin or its chromophore in the absence of dithiothreitol. For detectable levels of chromatin degradation, 10 ug/ml neocarzinostatin is required compared to only 2.5 ug/ml chromophore (expressed in ug equivalent neocarzinostatin). Such degradation also occurs more rapidly with chromophore than with neocarzinostatin. Digestion of chromatin with neocarzinostatin continues for at least 30 min at 37 C, while similar degradation caused by chromophore is complete in 1 min. Neocarzinostatin levels which actively degrade isolated chromatin can also effect release of soluble chromatin from intact nuclei. The released chromatin can serve as a substrate for micrococcal nuclease digestion. Such chromatin studies should prove useful in characterizing the mechanism of action of DNA reactive drugs such as neocarzinostatin. (Author abstract) (29 Refs)

52. RADIOIMMUNE ASSAY OF INDUCTION AND REMOVAL OF UV LESIONS IN TOTAL AND STAPHYLOCOCCAL NUCLEASE-RESISTANT DNA OF MAMMALIAN CHROMATIN.

McConlogue LC, Ward JF, Lewis HL, Norman A
Dept. Microbiology and Immunology, Univ. California, San Francisco, CA, 94143
Radiat Res; 89(2):381-395 1982

A direct lesion radioimmunoassay was used to measure induction and repair removal of UV lesions in total DNA (DNAt) and Staphylococcal nuclease-resistant DNA (DNAr). UV lesion induction in DNAr of HeLa and CHO cells was about 80% of that in DNAt. The two- to four-fold difference in repair synthesis observed in these DNAs cannot be accounted for by this result. The equal amounts of lesions per unit DNA in DNAr and DNAt of HeLa cells at 6 hr of repair induction can be explained by either the lower rate of lesion removal in staphylococcal nuclease-resistant DNA or complete nucleosomal rearrangement with respect to UV lesions during repair. (35 Refs)

53. X-RAY INHIBITION OF DNA SYNTHESIS AT DISCRETE TIMES DURING S PHASE IN SYNCHRONOUS HUMAN DIPLOID FIBROBLASTS.

Kapp LN, Painter RB
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Radiat Res; 89(2):424-427 1982

The incorporation of thymidine into irradiated and unirradiated diploid fibroblasts at various times during S phase was investigated. Results indicated that most replicons initiate during relatively restricted times in S phase. Results support a model of diploid fibroblast S phase that consists of multiple initiations of large numbers of replicons during short, specific times. (12 Refs)

54. CHANGES OF CHROMATIN STRUCTURE IN THYMOCYTES OF IRRADIATED RATS. IMMUNOCHEMICAL ANALYSIS.

Ermekova VM, Melkonian OS, Nazarova LF, Nanazashvili MG, Umanskii SR
Inst. Biological Physics, Pushchino, USSR
Radiobiologiia; 21(6):813-817 1981

To evaluate the mechanisms of DNA degradation in irradiated thymocytes, rats were irradiated with 1,000 rads, and chromatin and total nonhistone proteins (TNHP) were isolated from thymocytes. In another series of experiments, isolated chromatin was irradiated in vitro at 4,730 rads/min. Chromatin and TNHP were mixed with equal volume of complete Freund adjuvant and used for immunization of the rabbits. Immunochemical analysis showed that immune sera and isolated IgG formed specific complexes with chromatin. IgG isolated from the sera of nonimmunized rabbits did not react with chromatin. The products of chromatin degradation were significantly more active in reaction of complement fixation (RCF) than the control chromatin. In vitro irradiation of chromatin with 1,000 rads did not affect its reactivity in RCF; significant increase of the accessibility of antigenic determinants was detected only after irradiation with 20,000-50,000 rads. (8 Refs) (In RUS)

55. THE SENSITIVITY OF ACTIVE AND INACTIVE CHROMATIN TO IONIZING RADIATION-INDUCED DNA STRAND BREAKAGE.

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Div. Radiation Biology, Dept. Radiology, Case Western Reserve Univ., Cleveland, OH, 44106
Int J Radiat Biol; 41(1):71-77 1982

Sensitivity of Tetrahymena pyriformis strain GL-C DNA in actively transcribing and inactive states was compared with regard to gamma-radiation-induced single-strand break (SSB) induction. Following electrophoresis on agar gels and hybridization with poly(A+)RNA, nuclear DNA from irradiated cells was found in broader peaks and contained smaller fragments than did control DNA. In unirradiated cells, the profiles of transcribing and bulk DNA were similar, suggesting that transcribing genes are initially randomly distributed in all fragment sizes of nuclear DNA. Transcribing DNA from irradiated cells was found preferentially among the smaller fragments of total DNA. The apparent difference in the behavior of transcribing DNA from unirradiated and irradiated cells was not due to contamination of poly(A+)RNA with ribosomal RNA. The av mol wt of transcribing DNA was slightly but consistently greater than that of total nuclear DNA in unirradiated cells, while the reverse was true for irradiated DNA. When unirradiated nuclear DNA was mechanically sheared into fragment sizes comparable to those from irradiated cells, the similarity of the profiles of chromosomal and transcribing DNA was maintained after reduction of the fragment size of nuclear DNA. In vitro, no differences in the radiation sensitivities of transcribing and chromosomal DNA were observed. Kinetics of SSB rejoining are described. The results indicated that chromatin organization is important in the determination of the sensitivity of cellular DNA towards gamma-radiation. Not only yield but also the rate of repair of SSB is greater in actively transcribing genes than in the total nuclear DNA. (30 Refs)

56. EXCISION AND CROSSLINK REPAIR OF DNA AND SISTER CHROMATID EXCHANGES IN CULTURED HUMAN FIBROBLASTS WITH DIFFERENT REPAIR CAPACITIES.

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Gann Monogr Cancer Res; 27:33-44 1982

The relationship between sister chromatid exchange (SCE) induction and DNA repair was studied by evaluating the role of UV excision repair. The roles of interstrand crosslinking and repair in the induction of SCE in fibroblasts of xeroderma pigmentosum (XP) complementation groups (A to G and a variant group), Cockayne's syndrome (CS), and Fanconi's anemia (FA) with different repair capacities and predispositions to malignancies were studied. Killing sensitivities of the three types of cells to UV, 4-nitroquinoline-1-oxide (4NQO), and monofunctional decarbamoyl mitomycin C (DCMC) are reported. The XP groups were deficient in the initial steps of dimer excision repair in the order of A = G greater than C greater than D greater than D = F greater than variant. The extent of dimer-repair deficiency strictly determined the killing sensitivity of XP cells. Studies of the susceptibilities of XP and CS cells to SCEs induced by mutagens demonstrated that in the most defective XP group-A cells, the SCE induction rate by UV, 4NQO, and DCMC was a 3-5-fold higher than in normal cells. FA cells were approx 1.7x more sensitive to SCE induction by MC than normal cells and the SCE rate induced by DCMC was the same as that of normal cells. In XP cells, a six-fold higher SCE rate was observed after DCMC, and only a slightly higher SCE rate was observed after MC. Thus, part of cross-link damage may yield SCE. Caffeine synergistically increased UV-induced SCEs, but not UV-induced mutations in V79 cells, thus, dissociated SCE from mutation. (21 Refs)

57. EXCISION REPAIR OF DNA DAMAGE PRODUCED BY 4-NITROQUINOLINE 1-OXIDE IN CULTURED MAMMALIAN CELLS: ITS RELATION TO CARCINOGENESIS.

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Gann Monogr Cancer Res; 27:21-32 1982

Molecular mechanisms of repair of DNA lesions induced by 4-nitroquinoline 1-oxide (4NQO) in cultured mammalian cells were studied. In UV-irradiated xeroderma pigmentosum (XP) cells, the level of 4NQO-induced unscheduled DNA synthesis (UDS) was lowest in complementation group A, and increased in groups B, C, D, and E in order. In Cockayne's syndrome cells, normal levels of UDS after UV or 4NQO treatment were found. Epidermodysplasia verruciformis cells showed a slightly reduced level of UDS after UV irradiation and were highly sensitive to 4NQO. Variable responses to 4NQO were observed in cells of ataxia telangiectasia. The major 4NQO lesions produced in DNA of cultured human cells were a stable major 4NQO-guanine adduct, a stable minor 4NQO-guanine adduct, a stable major 4NQO-adenine adduct, and an unstable major 4NQO-guanidine adduct that releases 4-aminoquinoline 1-oxide upon hydrolysis. The excision repair of 4NQO-purine adducts from DNA of normal human cells and its absence in XP cells was demonstrated. Studies with mouse cells demonstrated that 4NQO-purine adducts are the major cause of 4NQO carcinogenesis. These findings are discussed with respect to excision repair, which may be important in chemical carcinogenesis. (49 Refs)

58. STRUCTURAL RELATIONSHIP BETWEEN A NORMAL CHICKEN DNA LOCUS AND THE TRANSFORMING GENE OF THE AVIAN ACUTE LEUKEMIA VIRUS MC29.

Robins T, Bister K, Garon C, Papas T, Duesberg P
Dept. Molecular Biology, Univ. California, Berkeley, CA, 94720
J Virol; 41(2):635-642 1982

We screened a recombinant chicken DNA/lambda phage library for sequences homologous to the transformation-specific sequences of the avian acute leukemia virus MC29 by hybridization with molecularly cloned MC29 proviral DNA. Three cellular DNA clones were found and compared with each other and with the viral genome by physical mapping with restriction endonucleases and by heteroduplex analysis. These experiments indicated that the three cellular clones overlap and represent a single cellular locus. The RNA genome of MC29 and normal cell DNA share a homologous region of 1.6 kilobases which is interrupted in the cellular DNA by 1.0 kilobase of sequences not present in the viral genome. Hybridization of the cloned cellular DNA to viral RNA and analysis of the protected viral RNA by fingerprinting techniques indicated that there is extensive sequence homology between the helper virus-unrelated mcv sequences of the viral RNA and the cellular DNA, with only minor base differences. The cellular mcv locus, however, lacks all helper virus-related sequences of MC29, including those of the partial viral gag gene which, together with mcv, encodes the probable transforming protein of MC29. We conclude that although the mcv locus of the normal cell does not represent a complete structural homolog to the onc gene of MC29, it is probably the precursor to the onc-specific sequence in the virus. (Author abstract) (27 Refs)

59. EXCISION OF POLYOMA VIRUS GENOMES FROM CHROMOSOMAL DNA BY HOMOLOGOUS RECOMBINATION.

Lania L, Boast S, Fried M
Istituto di Biologia Generale e Genetica, Universita di Napoli, Napoli, Italy
Nature; 295(5847):349-350 1982

Excision of polyoma virus genomes from chromosomal DNA was examined in five polyoma-transformed rat cell lines. One cell line contains multiple inserts of integrated viral sequences, free viral genomes and at least one complete early region containing an intact coding region for the polyoma large T antigen (T-Ag). Other four lines do not contain free viral forms or an intact coding region for the polyoma large T-Ag. All five lines contain intact coding regions for the small and middle T-Ag species. All five lines were fused either to themselves or to mouse cells and the fused cells were assayed for free viral forms (at varying times) or the production of infectious virus (after 5 days). In the self-fused cells, free viral forms were found only in the polyoma-rat cells; no virus was detected (less than 50 plaque-forming units/10(6) cells) in the self fusion of the polyoma-rat cells. The production of both free viral genomes and infectious virus was detected after fusion to mouse cell of polyoma-rat and two lines containing partial duplications of viral sequences. In the two lines that did not contain partial duplications of viral sequences, no free viral forms or infectious virus could be detected after fusion to mouse cells. In the fusions of 2b-C3 and 53-rat with mouse cells, the amount of viral DNA and infectious virus produced appears to be related to the amount of duplicated viral sequences present, suggesting that the excision may be a function of the target size for possible recombination events as has been observed in other systems. (32 Refs)

60. DOUBLE MINUTES IN MOUSE NEUROBLASTOMA CELLS AND THEIR HYBRIDS.

Kano-Tanaka K, Higashida H, Fukami H, Tanaka T
Lab. Cell Biology, Aichi Cancer Center Res. Inst., Chikusa, Nagoya 464, Japan
Cancer Genet Cytogenet; 5(1):51-62 1982

Cytogenetic studies were carried out on three clones of mouse neuroblastoma cells and six interspecific hybrid cells derived from the mouse neuroblastoma cells with either rat glioma cells and liver cells or Chinese hamster brain cells. The hybrid cells possessed characteristic karyotypes with marker chromosomes originating from the neuroblastoma cells. The parental chromosome constitution in the hybrid cells was clone-specific, even in the clones derived from the same parental cells. Double minutes (DMS) were demonstrated in the neuroblastoma cells and in all the hybrid cells studied. In addition other chromosome aberrations, such as microchromosomes and chromosome pulverization, were also observed in these cells. DMs varied in number and morphology among the cells. The number of DMs per cell correlated positively with the level of ploidy and with the karyological constitution contributed by the parental neuroblastoma cells. The results indicate that DMs have a chromosome nature and that the DMs of neuroblastoma chromosomes were transferred into the hybrid cells. (Author abstract) (34 Refs)

61. DOUBLE MINUTES IN HUMAN TUMOR CELLS.

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Dept. Human Genetics, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, CT, 06510
Cancer Genet Cytogenet; 5(1):81-94 1982

The role of double minutes (DM) in the biology of cancer cells was investigated. DM and homogeneously staining regions (HSR) are found in cells selected for resistance to certain antimetabolites and in unselected human and murine tumor cells. DM are small chromatin particles that replicate and segregate in the absence of centromeres. DM and HSR as drug resistant mutants show wild-type proteins, but the specific activity of the target enzyme greatly exceeds that of sensitive cells. Pale staining with C-banding suggested that DM lacked constitutive heterochromatin. Unequal distribution of DM at mitosis due to the lack of centromeres causes DM numerical heterogeneity. HSR is a distinctive region on a long marker chromosome. Cytologic hallmarks of DM in untreated cells include: peripheral location on the hollow spindle at metaphase, clustering of DM in a nucleolus like matrix at metaphase and anaphase, association of DM clusters to telomeres at metaphase and anaphase, absence of a DM condensation cycle during mitosis, nondisjunction of DM such that they appear double throughout mitosis, and micronuclei in some cells at telophase. Amplification of the dihydrofolate reductase gene is not represented by DM from tumors in untreated patients, although the possibility of gene amplification unrelated to methotrexate treatment remains. Effects of either DM or HSR on malignancy or on the progression of normal development have to be explored. (105 Refs)

62. THE RAT XC SARCOMA CELL LINE: RIBOSOMAL RNA GENE AMPLIFICATION AND BANDED KARYOTYPE.

Tantravahi U, Erlanger BF, Miller OJ
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Cancer Genet Cytogenet; 5(1):63-73 1982

Ribosomal RNA gene amplification has been demonstrated in the rat XC sarcoma cell line. Cells of this rat line have a fairly stable karyotype with several unusual features, which have been clarified by in situ hybridization, silver staining, and binding of antibodies to 5-methylcytosine. There are one or two tiny acrocentric chromosomes containing transcriptionally active 18S and 28S ribosomal RNA (rRNA) genes. The short arm of one chromosome No 12 has been replaced by a GC-rich, C-band negative, differentially staining region (DSR) containing an increased number of rRNA genes; most of these are transcriptionally inactive and located in regions containing highly methylated DNA. The short arm of a small chromosome, probably a No 20, has been replaced by a GC-rich, C-band negative, homogenously staining region (HSR) that presumably represents amplification of a DNA sequence other than the 18S and 28S rRNA coding sequences. The DNA in this HSR is not enriched in 5-methylcytosine and neither is that in the HSRs of methotrexate-resistant Syrian hamster cells. (Author abstract) (40 Refs)

EFFECTS OF EXOGENOUS AGENTS ON CHROMOSOMES

63. FAILURE TO DEMONSTRATE AN EFFECT OF IN VIVO DIAGNOSTIC ULTRASOUND ON SISTER CHROMATID EXCHANGE FREQUENCY IN AMNIOTIC FLUID CELLS.

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Am J Med Genet; 11(1):31-35 1982

In vivo effects of clinical doses of ultrasound (PICKER digital B-scanner) on sister chromatid exchange (SCE) in amniotic fluid cells were investigated. Forty women in the second and third trimester of pregnancy were divided into control (no ultrasonography before amniocentesis), and experimental (ultrasonography followed by amniocentesis), groups. Following amniocentesis, cells were cultured and examined for SCE. Frequency was determined only in cells with 46 chromosomes. Results show second and third trimester SCE frequencies of 6.4-10.4 and 5.7-10.4, respectively, compared to SCE frequencies of 6.3-8.9 in the controls. Neither second or third trimester women showed a dose response tendency and all SCE rates fell into the previously reported normal range of control values (3.0-12.7). Limitations of the study include: lack of uniformity in ultrasound dose delivered to amniocytes, length of incubation time required prior to SCE analysis, quiescent state of amniotic fluid fibroblasts, and the clonal nature of amniocytes in culture. Apparently no long-term elevation in the SCE frequency occurs in amniocytes following in vivo ultrasound exposure. (14 Refs)

64. SISTER-CHROMATID EXCHANGES IN MOUSE EMBRYOS AFTER EXPOSURE TO ULTRASOUND IN UTER O.

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Biology Div., Oak Ridge Natl. Lab., P.O. Box y, Oak Ridge, TN, 37830

Mutat Res; 103(3-6):315-320 1982

Embryos from Swiss albino mice at 11 +-1 day (embryonic stage) and 15 +-1 day (fetal stage) of pregnancy were exposed in utero to bromodeoxyuridine (BrdU) by sc implantation of a 55 mg tablet, and irradiated with ultrasound (0-0.67 Watts/square cm) while immersed in 34 C water. Neither the embryo or the fetus groups of embryonic mice exhibited elevated sister-chromatid exchange frequency in bone marrow cells when compared to maternal bone marrow cells. There were no age-dependent or dose-dependent effects. (18 Refs)

65. FREQUENCY OF ABERRATIONS IN MONO- AND DI-5-BROMODEOXYURIDINE SUBSTITUTED CHROMATIDS.

Antoshchina MM, Poriadkova NA, Luchnik NV
Res. Inst. Medical Radiology, Obninsk, USSR
Genetika; 17(12):2167-2171 1981

The effect of bromodeoxyuridine (BDU) on chromatid radiosensitivity was studied in cultured Chinese hamster fibroblasts and human lymphocytes. The cells were incubated with the BDU for two cell cycles; at stage G2 of the second mitosis, the cells were irradiated with 60Co gamma rays (40 rads/min, total dose 100 rads). Harlequin staining showed that the number of breaks in light (disubstituted) regions was significantly lower than that in dark (monosubstituted) regions. (8 Refs) (In RUS)

66. THE ACTION SPECTRUM (313-435 NM) FOR KILLING HOECHST 33258 TREATED CHINESE HAMSTER OVARY CELLS CONTAINING BROMODEOXYURIDINE SUBSTITUTED DNA.

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Photochem Photobiol; 35(2):163-166 1982

The action spectrum (313-435 nm) for killing Chinese hamster ovary cells containing bromodeoxyuridine substituted DNA and treated with Hoechst 33258 was very similar to the absorption spectrum of the dye bound to chromatin, indicating that sensitization was mediated through direct absorption of radiation by the dye. The ratio of sensitization cross sections for 365 nm (plus dye) to 313 nm (no dye) was approx 30 while this ratio for strand breakage was about one. These results are in agreement with the hypothesis that strand breaks are not the major class of lethal photoproducts induced via Hoechst 33258 sensitization. (Author abstract) (15 Refs)

67. SISTER-CHROMATID EXCHANGES AND CELL-CYCLE DELAY IN CHINESE HAMSTER V79 CELLS TREATED WITH 9 ORGANOPHOSPHORUS COMPOUNDS (8 PESTICIDES AND 1 DEFOLIANT).

Chen HH, Sirianni SR, Huang CC
Dept. Experimental Biology, Roswell Park Memorial Inst., Buffalo, NY, 14263
Mutat Res; 103(3-6):307-313 1982

Rapidly growing Chinese hamster V79 cells, pretreated with 5-bromodeoxyuridine (10 ug/ml), were treated with nine organophosphorus compounds in doses ranging from 10-80 ug/ml or 2.5-20 ug/ml. Significant increases in sister-chromatid exchanges (SCEs) were observed only in cultures treated with O,O-dimethyl O-[3-methyl-4-(methylthio)phenyl] phosphorothioate (Fenthion) at 40 and 80 ug/ml and S-[2-(ethylsulfinyl)ethyl]-O,O,-dimethyl phosphorothioate (oxydemeton-methyl) at 80 ug/ml. All compounds except O,O-diethyl O-[4-(methylsulfinyl)phenyl] phosphorothioate (Fensulfothion) and oxydemeton-methyl caused cell cycle delay in a dose-dependent fashion. O,O-dimethyl-S-[(4-oxo-1,2,3-benzotriazin-3(4H)-yl) methyl] phosphorodithioate (Azinphos-methyl: 40 and 80 ug/ml) did not induce SCEs, but was highly toxic to V79 cells. Pesticides not producing SCEs are recommended as substitutes for those that do when distribution in the natural environment is contemplated. (9 Refs)

68. THE DISTRIBUTION OF INDUCED SISTER-CHROMATID EXCHANGES: A TOOL FOR IDENTIFYING AGENTS DIRECTLY INTERACTING WITH DNA.

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Mutat Res; 103(3-6):333-337 1982

Exponentially-growing V79-AP4 Chinese hamster cells were treated for 1 hr with the direct alkylating agent ethyl methanesulfonate (EMS: 1) and 10 milliM and the DNA-synthesis inhibitors 5-bromodeoxyuridine (BUdR: 0.4, 0.8, 1.6 milliM) and aphidicholine (APC: 5, 10, 20 ug/ml). THe frequency distributions of sister-chromatid exchanges (SCEs) were not changed after EMS, although the mean number of SCEs increased with concentration. With BUdR and APC the median SCE/cell was about the same for all concentrations, but the spread of the frequency distribution was markedly increased as concentrations of both agents increased. Comparing SCE distribution patterns in this manner makes it possible to determine whether SCEs were induced by factors inside DNA (damaged template, EMS) or outside DNA (damaged replication machinery, BUdR, APC). (11 Refs)

69. DIFFERENT EFFECTIVENESS OF HYPERTHERMIA WITH REGARD TO FAST ELECTRONS AND X-RAYS WITH DIFFERENT ENERGY SPECTRA.

Schrader-Reichhardt U, Markus B
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Strahlentherapie; 157(8):544-552 1981

The synergistic enhancement of the irradiation effect by mild (40.5 C) and strong (43 C) hyperthermia (TER = temperature enhancement ratio) was examined for different sparsely ionizing radiation qualities (15 MeV electrons in two irradiation depths corresponding to a relative depth dose of 100% and 30%, 200-kV and 29-kV-x-rays). Hypotetraploid ('4n') and diploid (2n), asynchronous, exponentially growing CHO fibroblasts were used as experimental subjects. The survival in the colony test was used as criterion to assess the effect. The experiments carried out with 4n cells showed that, for the two temperatures, the TER decreases with increasing ionization density, and, when applying fast electrons producing an extremely sparse ionization in an irradiation depth of 100%, the TER shows a maximum increase as compared to the more densely ionizing radiation qualities. Already when mild hyperthermia is employed, fast electrons show a TER of 1.25 which rises to about 2.25 at 43 C. In case of 29-kV-x-rays, these values amount to 1 and 1.66 respectively. As to the 2n cells, the TER reaches here the double value and seems to be similarly dependent on the ionization density. (Author abstract) (41 Refs) (In GER)

70. RADIOTHERAPEUTICALLY INDUCED CHROMOSOME ABERRATIONS: STUDIES IN 'BIOLOGICAL DOSIMETRY'.

Kuttner-May S, Traut H
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Strahlentherapie; 157(9):607-612 1981

The yield of chromosome aberrations (dicentric chromosomes, ring chromosomes) induced in lymphocytes of four radiotherapy patients was determined. In each case this yield was drastically increased when compared with the spontaneous incidence, the dicentric frequencies increasing by the following factors: 604, 525, 600 and 725. With the aid of the dicentric yield obtained, the following equivalent whole body doses were estimated ('biological dosimetry'): 309, 286, 308 and 341 rd. Comparing the observed with the theoretical number of cells with 0, 1, 2, 3 etc dicentrics ('distribution analysis'), we found a highly significant departure from the Poisson distribution, as was to be expected after partial body irradiation. The distribution analysis seems principally suited to discriminate between partial and whole body irradiation. (Author abstract) (25 Refs) (In GER)

71. CORRELATION OF CHROMOSOME PATTERNS IN HUMAN LEUKEMIC CELLS WITH EXPOSURE TO CHEMICALS AND/OR RADIATION. PROGRESS REPORT, JANUARY 1, 1981-DECEMBER 31, 1981.

Rowley JD

Chicago Univ., Chicago, IL

Correlation of Chromosome Patterns in Human Leukemic Cells with Exposure to Chemicals and/or Radiation. Progress Report, January 1, 1981-December 31, 1981. Available from National Technical Information Service, Springfield, VA, as DE81028158:, 11 pp., 1981.

The overall aim is to determine whether there is a relationship between exposure to radiation, environmental pollutants, and/or genetic background and the development of ANLL or other hematologic malignancies. I will try to define the factors that influence the development of ANLL as a second malignancy in patients who have been exposed to large doses of radiotherapy and/or chemotherapeutic agents. Two long-term goals are (1) to identify the genes that are located at the sites of consistent translocations, and then to determine the alterations in gene function that are associated with these translocations and (2) to establish the baseline frequency of various chromosome changes (mutations) in myeloid cells and then to analyze the influence of various types of environmental exposure or medical treatment on the baseline mutation rate. Ultimately, it may be possible to determine the extent of mutagenic exposure in various populations through an analysis of the leukemic cells of those populations. (Author abstract)

72. MICRODOSIMETRY OF LYMPHOCYTES IRRADIATED BY ALPHA PARTICLES.

Fisher DR, Harty R

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Proceedings of the Annual Scientific Meeting of the Radiation Research Society, held in Minneapolis, MN, May 31, 1981.-3Available from National Technical Information Service, Springfield, VA, as DE81030090: 26 pp., 1981.

This paper reports the use of internal microdosimetry techniques to reinvestigate the dosimetry of two very similar experiments with apparently contradictory dose-response results. Yields of dicentric chromosome aberrations induced in human blood lymphocytes following in vitro exposure to dissolved americium or plutonium at two separate laboratories produced linear dose-response functions, but the slopes of the best-fit straight lines differed by a factor of 12. Our microdosimetric analysis showed the results of one experiment to be inconsistent with a uniform distribution of activity. It also showed that the difference in slope could be attributed to differences in particulate size and spatial distribution as a result of dissimilarities in procedures used for preparing the actinide solutions. (Author abstract)

73. YIELD OF CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES TREATED WITH 5-FLUORODEOXYURIDINE ALONE AND IN COMBINATION WITH GAMMA RADIATION: CHANGES IN THE RESPONSE DURING THE MITOTIC CYCLE.

Poriadkova NA, Izmailova NN, Luchnik NV
Res. Inst. Medical Radiology, Obninsk, USSR
Genetika; 17(12):2212-2219 1981

The chromosome-modifying effect of 5-fluorodeoxyuridine (FDU) was studied in cultured human lymphocytes. The cells were irradiated with 50 or 100 rads and, immediately afterward were placed in medium containing the FDU (2 x 10(-7) M) for 2.5 hr. Cytogenetic analysis showed that exposure of the cells to FDU alone increased the yield of chromosome aberrations at the end of stage G1 and in stage G2. The yield of chromosome aberrations after exposure to FDU in combination with irradiation was similar to that after exposure to either the FDU or the radiation alone. These findings indicate that the pseudomutagenic effect of FDU is associated with the inhibition of repair of spontaneous or radiation-induced aberrations. (27 Refs) (In RUS)

74. X-RAY-INDUCED CHROMOSOME DAMAGE IN LIVE MAMMALIAN CELLS, AND IMPROVED MEASUREMENTS OF ITS EFFECTS ON THEIR COLONY-FORMING ABILITY.

Joshi GP, Nelson WJ, Revell SH, Shaw CA
Dept. Physics, Inst. Cancer Res., Sutton, Surrey, England
Int J Radiat Biol; 41(2):161-181 1982

We have improved the precision of the technique described by Grote et al for the observation of the radiation responses of live cultured mammalian cells with an incubated phase-contrast microscope: the colony-forming abilities of single cells obtained by selective detachment of mitoses (instead of cell pairs as previously) may now be followed individually and may be directly compared with chromosome damage detected after post-radiation mitosis (M1). An x-ray dose of 1.4 Gy to diploid Syrian hamster cells (BHK 21 C13) in G1 had no effect on cell ability to reach M1. If chromosome fragment loss was then detected (as micronuclei) in the daughter-cell pair then colony-forming ability nearly always deteriorated, and either a stop-growth (79%) or a slow-growth (21%) colony resulted; but chromosomal bridges which persisted beyond M1 broke during interphase 1 and themselves caused no detectable cell damage additional to that attributable to the micronuclei which accompanied them. (Author abstract) (30 Refs)

75. NOTES ON CYTOGENETIC EFFECTS OF IRRADIATION ON THE OOCYTES AT MEIOTIC STAGES IN THE CHINESE HAMSTER.

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Dept. Genetics, Inst. Developmental Res., Aichi Prefectural Colony, Kasugai 480-03, Japan

Proc Jpn Acad [B]; 57(7):244-247 1981

Cytogenetic effects of x-irradiation were studied in meiotic stages of primary oocytes of 24-30-wk-old female Chinese hamsters. Frequency of chromosome aberrations following 200 R x-irradiation is presented (33.8% were structural aberrations represented by fragments and chromatid breaks, 6.3% included numerical aberrations involving heteroploidy and diploidy, and 7.7% included both structural and numerical aberrations). Frequency of oocytes with chromosome aberrations was higher in the group exposed in the late afternoon of the 1-day interval than in other groups. (11 Refs)

76. METAPHASE I DELAY AS A FACTOR INFLUENCING TRANSLOCATION YIELD FROM SPERMATOLOGICAL IRRADIATION IN MICE CARRYING ROBERTSONIAN TRANSLOCATIONS.

Crocker M
Radiobiology Unit, Medical Res. Council, Harwell, Didcot, Oxon Ox 11 ORD, England
Mutat Res; 103(3-6):339-343 1982

Male mice from MC, RIB, and 3H1 lines were exposed to 500 R x-rays, and cytological preparations of their testes examined. the proportion of translocations that involve metacentrics at metaphase I was compared to the proportion expected to be induced in the spermatogonia assuming random exchange between metacentrics and acrocentrics, and the number and size of clones of acrocentrics and metacentrics was determined from preparations of individual tubules. Both methods of analysis showed that the fre quency of metacentric translocations was enhanced at metaphase I. The greater clone size of the metacentric translocations compared with clone size of acrocentric translocations compared with clone size of acrocentric translocations indicates enhancement was due to events occurring before induction. The data support the hypothesis that spermatocytes bearing translocations take longer to pass through metaphase I, causing a spurious enhancement of the yield of translocations observed at this stage, and accounting for the difference in results between metaphase I observations and those made in F1 offspring. (8 Refs)

77. MONITORING GENOTOXICITY IN THE OCCUPATIONAL ENVIRONMENT.

Sorsa M, Falck K, Norppa H, Vainio H
Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Scand J Work Environ Health; 7(Suppl4):61-65 1981

The urinary mutagenicity assay and analysis of structural chromosome aberrations and sister chromatid exchanges in cultured lymphocytes were used to detect exposure to genotoxic chemicals in various job categories in the rubber industry and in oncology units at hospitals. The urine of workers in the rubber industry had significantly increased mutagenic activity after one week work in comparison to values obtained after vacation. Oncology nurses had a significantly higher mean sister chromatid exchange frequency than office personnel, but a value similar to that of other hospital nurses. (14 Refs)

78. BIOLOGICAL MARKERS FOR CHEMICAL EXPOSURE.

Maugh TH
No affiliation given
Science; 215(4533):643-647 1982

The health problems associated with hazard waste storage and dump sites are discussed with special emphasis on the ways to monitor the chemical exposure and to assess the long-term health effects. Difficulties encountered in the assessment of chromosome aberrations and sister chromatid exchanges, reproductive abnormalities, and neurotoxic effects are outlined, and the need for long-term monitoring of the population at risk is emphasized. (3 Refs)

79. ANTINEOPLASTIC AGENTS AS POTENTIAL CARCINOGENS: ARE NURSES AND PHARMACISTS AT RISK?

Reich SD
Univ. Massachusetts Medical Center, Worcester, MA
Cancer Nurs; 4(6):500-502 1981

Adverse effects on nurses and pharmacists exposed to antineoplastic drugs are described in relation to problems associated with epidemiological studies, mutagenesis and chromosomal analysis, and clinical studies. No hard evidence seems to suggest that personnel exposed to oncology drugs during the process of preparation and administration have a greater incidence of cancer than the general population. Evidence that these people are in an environment with greater mutagenic potential than other hospital workers is also limited. (21 Refs)

80. STUDIES ON MUTAGENIC EFFECT OF ENVIRONMENTAL FACTORS IN NONFERROUS METALLURGICAL PLANTS.

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Zaklad Biologii Ogolnej, Instytut Biologiczno-Morfologiczny Slaskiej Akademii Medycznej, ul. K. Marksa 19, 41-808 Zabrze, Poland
Patol Pol; 32(2):263-268 1981

Chromosome aberrations in peripheral blood lymphocytes were studied in 32 workers occupationally exposed to nonferrous metals: (15 lead, 11 cadmium, 6 zinc). The numbers of aberrant cells and of structural chromosome aberrations in the workers showed variations from one worker to another, but the mean values showed an increase, compared with nonexposed controls. Especially significant differences were observed in the structural rearrangements (dicentric chromosomes and translocations), as well as disturbances in spiral formations. The frequency of sister chromatid exchanges (SCE) in lymphocytes showed a decrease in the workers compared with controls. This decrease in the workers may be related to the mutational senescence of cells. The results indicate that the synergistic effect of the different metals can induce chromosome mutations under the conditions of long-term exposure in vivo. (no Refs) (In POL)

81. DIESEL-EXHAUST-PARTICLE EXTRACT ENHANCEMENT OF CHEMICAL-INDUCED MUTAGENESIS IN CULTURED CHINESE HAMSTER OVARY CELLS: POSSIBLE INTERACTION OF DIESEL EXHAUST WITH ENVIRONMENTAL CARCINOGENS.

Li AP, Royer RE
Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., P. O. Box 5890, Albuquerque, NM
Mutat Res; 103(3-6):349-355 1982

Dichloromethane extracts of exhaust particles (EP) filtered from the exhaust of diesel passenger cars of five different manufacturers were tested in combination with known mutagens using the Chinese hamster ovary (CHO) hypoxanthine-guanine phosphorylase assay. N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG: 0.5 ug/ml) and benzo(a)pyrene [B(a)P: 0.5 ug/ml] were administered with and without diesel EP extract (60 ug/ml in dimethyl sulfoxide) to CHO cells grown with and without Aroclor 1254-induced rat-liver S9 activator. Mutagenicity of the EP extract alone was uniformly low, but treatment of CHO cells with mutagen plus EP extract consistently yielded a mutant frequency higher than expected. Without S9 activation, combined treatment of EP + MNNG gave a mutant frequency 1.4-1.9 x higher than expected. With S9 activation the EP +

B(a)P treatments resulted in an observed mutation frequency 2.8-3.2 x the expected value. The observed enhancement phenomenon is highly reproducible, and also affects sister-chromatid exchanges and mutation to ouabain resistance. (21 Refs)

82. CHROMOSOME ABERRATIONS IN CULTURED HUMAN LYMPHOCYTES EXPOSED TO TRIVALENT AND PENTAVALENT ARSENIC.

Nordenson I, Sweins A, Beckman L
Dept. Medical Genetics, Univ. Umea, S-901 85 Umea, Sweden
Scand J Work Environ Health; 7(4):277-281 1981

When human lymphocytes were cultured in concentrations of trivalent (As3) and pentavalent arsenic (As5) comparable to concentrations found in the urine of copper smelter workers, significantly increased frequencies of chromosome aberrations (gaps, chromatid breaks and exchanges, sister chromatid exchanges) were found after exposure to As3, but not As5. This effect was not found when G0 lymphocytes were exposed to As3. (18 Refs)

83. INTAKE, FORMATION, AND RELEASE OF MUTAGENS BY MAN.

Stich HF, Rosin MP, San RH, Wu CH, Powrie WD, Van Soest PJ, Wattenberg LW, Watson JD, Tannenbaum SR, Wilkins TD, Magee PN, Bruce WR
Environmental Carcinogenesis Unit, British Columbia Cancer Res. Centre, Vancouver, British Columbia V5Z 1L3, Canada
Banbury Rep; 7:247-266 1981

The incidence of stomach cancer was high in Japan during the Edo period of its history, when foodstuffs were not contaminated by industrial or agricultural chemicals. During the past several decades, when the uses of these chemicals increased in Japan and elsewhere, the incidences of cancer of the stomach, esophagus, and mouth in Japan declined steadily. Many classes of compounds occurring in fresh, cooked, and stored foodstuffs have been identified as mutagens. The use of food additives, pesticides, and herbicides will undoubtedly add to the mutagenic load of foodstuffs. The available evidence raises several questions: whether foodstuffs comprise the major source of mutagens (and, by implication, carcinogens) in the human body; why the cancer frequency is so low, despite this daily intake of mutagens; and why DNA repair-deficient patients (eg, those with xeroderma pigmentosum) develop skin cancers at an early age but lack a comparable frequency of gastrointestinal cancers. It is difficult to discard the idea that people always ingest enough carcinogens to produce neoplastic cells, but that the occurrence of this event is enhanced or suppressed by genetic factors, whose role may be greater than hitherto assumed. If mutational events are involved at all in tumor initiation, they may not be the types of events detected by the in vitro bioassays now used. The number of different mutagens in food products, digested foods, and feces is evidently very large. The genetic damage in somatic cells may be the product of the actions of many mutagens rather than of one predominating substance. (31 Refs)

84. GENOTOXICITY OF COCOA EXAMINED BY MICROBIAL AND MAMMALIAN SYSTEMS.

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Inst. Biochemistry, Federal Res. Centre for Nutrition, Engesserstr. 20, D-7500 Karl 5 ruhe, W. Germany
Mutat Res; 103(3-6):275-281 1982

The bone marrow sister-chromatid exchange (SCE) test, performed with implanted 5-bromodeoxyuridine tablets; the micronucleus test performed with outbred 10 to 14 wk-old Chinese hamsters; and the Ames test with Salmonella typhimurium (strains TA1535, TA100, TA1537, TA1538, TA98) were used to evaluate the genotoxicity of cocoa and two of its constituents: theobromine (ThB) and caffeine (CA). Not roasted cocoa administered by stomach tube at doses of 0.1-0.6 g/animal caused a dose-dependent elevation of bone-marrow SCEs; roasted cocoa (chocolate liquor) gave almost identical results. Extraction of the fat (47% of cocoa) almost doubled the number of SCEs at the highest cocoa dose, to 10.01/cell, and increased the number of SCEs at all other doses somewhat less (range 5.33-7.88 SCEs/cell). Cocoa butter and ThB- and fat-free cocoa caused no significant elevation of SCEs. ThB alone at doses of 2.5-20 mg/animal, and ThB + CA (6:1) at the same doses caused similar high levels of SCEs (4.77-9.50) in a dose-dependent way. The micronucleus test was negative for roasted and fat-free cocoa, 0.6 g/animal, but highly positive for ThB (doses 2 x 20, 30, or 40 mg ThB), but ThB (dose 1 x 20, 30, or 40 mg/animal) gave negative results in the chromosome aberration test. None of the Salmonella strains showed any mutagenic effect of cocoa at concentrations of 5.0, 2.5, 1.0, and 0.5%; greater than or equal to 5.0% cocoa was antibacterial. ThB at 0.25% gave no evidence of mutagenicity with or without metabolic activation. ThB is evidently not demethylated in all mammals, and hence its non-mutagenicity cannot be assumed. (16 Refs)

85. ABNORMAL CELL DIVISION IN CULTURED HUMAN FIBROBLASTS AFTER EXPOSURE TO DIETHYLSTILBESTROL.

Danford N, Parry JM
Dept. Genetics, Univ. Coll. Swansea, Swansea SA2 8PP, England
Mutat Res; 103(3-6):379-383 1982

Five doses of diethylstilbestrol dipropionate (DES: 5-25 ug/ml) were administered to cells of the human foreskin fibroblast cell line HSBP is slide cultures, and the anaphase and telophase stages were examined after Giemsa staining. No abnormalities were observed in cells treated with 5 ug/ml DES, but among the 10 ug/ml-treated cells a number had cytoplasm dividing into two, but without chromosomes being separated to opposite poles of the cell. The chromosomes in these cells were often at the end away from the dividing plant in the cytoplasm, suggesting migration to one pole only. Presumed intermediate stages in this abnormality were seen. Cells treated with 15-25 ug/ml DES had no normal anaphases, but did have many cells with this new cytoplasmic cleavage abnormality, as well as some cells with condensed chromsomes indicating metaphases, and others with micronuclei. Defects of the spindle, centriole, cell metabolism, or centromeres are possible causes of the effect reported here, but further studies are needed to elucidate the precise mechanism. (11 Refs)

86. MICRONUCLEUS TEST IN VICIA FABA ROOT TIPS TO DETECT MUTAGEN DAMAGE IN FRESH-WATER POLLUTION.

Degrassi F, Rizzoni M
Institute Genetics, Faculty Sciences M.F.N., Univ. City, 00185 Rome, Italy
Mutat Res; 97(1):19-33 1982

The pattern of micronucleus frequency was compared with that of chromosome aberrations and mitotic anomalies in relation to mechanism of action of the mutagen, dose, exposure time, and time between treatment and fixing. Root tips were subjected to a range of doses of x-rays, mitomycin C, methyl methanesulfonate, ethidium bromide, or colchicine. All treatments caused dose-dependent responses, both in chromosome anomalies and micronucleus generation. Generally micronuclei-generating events were more frequent 2-3 cycles before the peak in micronuclei was apparent. Where short and long exposure times yielding the same total dose were used, the longer time was both more mutagenic and more toxic. Control levels of chromosomal and mitotic anomalies and micronuclei numbers were always low. Micronucleus frequency was directly proportional to mitotic index and to both chromosomal and mitoclastic generating events, regardless of the mechanism of action of the agent employed. Micronucleus frequency is a more sensitive indicator than frequency of generating events observed in mitosis, particularly with low doses and weak mutagens. (33 Refs)

87. CYTOGENETIC EFFECTS OF BC AND 4CMB IN THE MOUSE EVALUATED BY THE MICRONUCLEUS TEST.

Hartley-Asp B

Pharmacology Dept., AB Leo Res. Lab., Box 941, S-251 09 Helsingborg, Sweden

Mutat Res; 100(1-4):373-374 1982

In vivo mutagenicity of 4-chloromethylbiphenyl (4CMB) and benzyl chloride (BC) was measured in SPF NMRI female mice using the micronucleus assay. Various doses of the test compounds were injected ip in two fractions. 4CMB was 10x as toxic as BC in test animals. Neither compound increased the frequency of micronuclei in polychromatic erythrocytes. (no Refs)

88. ASSAY OF THE INDUCTION OF MITOTIC CROSSING-OVER AND ANEUPLOIDY IN YEAST BY BC, 4CMB AND 4HMB.

Parry JM

Dept. Genetics, Univ. Coll. Swansea, Swansea SA2 8PP, Wales

Mutat Res; 100(1-4):139-143 1982

Abilities of benzyl chloride (BC), 4-chloromethylbiphenyl (4CMB), and 4-hydroxymethylbiphenyl (4HMB) to induce mitotic crossing-over and mitotic chromosome aneuploidy were assayed in strain D6 of Saccharomyces cerevisiae. Only BC and 4CMB produced mitotic crossing-over. Addition of S9 mix reduced the toxicity and genetic activity of both compounds. Neither 4CMB, 4HMB, nor BC induced mitotic chromosome aneuploidy. (3 Refs)

89. THE EFFECT OF 4CMB ON GERM CELLS OF THE MOUSE.

Brook JD

MRC Clinical and Population Cytogenetics Unit, Western General Hosp., Edinburgh EH4 2XU, Scotland

Mutat Res; 100(1-4):305-308 1982

The effects of 4-chloromethylbenzine (4CMB) on meiosis were studied in oocytes and spermatocytes of Swiss mice. Females were superovulated. Germ cells were exposed to 4CMB during metaphase I and examined during metaphase II. Determination of chromosome numbers indicated that 4CMB did not increase aneuploidy in the germ cells relative to controls. (5 Refs)

90. 4-CHLOROMETHYLBIPHENYL (4CMB) - AN IN VIVO CYTOGENETIC STUDY IN THE CHINESE HAMSTER (CRICETULUS GRISEUS).

Albanese R

Pharmaceuticals Div., Imperial Chemicals Ltd., Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG, England

Mutat Res; 100(1-4):309-312 1982

The clastogenic potential of 4-chloromethylbiphenyl (4CMB) was studied in bone marrow cells from Chinese hamsters. In acute and subacute trials no significant differences in the frequency of chromosomal damage were found between cells from 4CMB-treated animals and cells from control animals. Aberrations in the 4CMB-treated group occurred at low frequency, but included severe types of damage (exchange figures and dicentric chromosomes). (2 Refs)

91. INVESTIGATION OF THE CYTOGENETIC EFFECTS OF 4-CHLOROMETHYLBIPHENYL (4CMB) ON CULTURED RAT-LIVER CELLS.

Hodson-Walker G, Moore LJ, Dance J, Dean BJ

Shell Toxicology Lab. (Tunstall), Shell Res. Ltd., Shell Res. Centre, Sittingbourne, Kent ME9 8AG, England

Mutat Res; 100(1-4):283-285 1982

Induction of structural chromosomal aberrations (CA) by 4-chloromethylbiphenyl (4CMB) was studied in RL4 rat-liver cells. Positive control material was exposed to 7,12-dimethylbenzanthracene. 4CMB produced significant CA at concentrations greater than 5 ug/ml; 100% of cells showed some form of CA at 20 ug/ml. CA included chromatid gaps, chromatid aberrations, and polyploidy. (2 Refs)

92. THE EFFECTS OF 4CMB, 4HMB, AND BC ON SCE, CHROMOSOME ABERRATION AND POINT MUTATION IN CULTURED CHINESE HAMSTER OVARY CELLS.

Phillips BJ, James TE

British Industrial Biological Res. Assoc., Woodmansterne Road, Carshalton, Surrey SM5 4DS, England

Mutat Res; 100(1-4):263-269 1982

Mutagenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was studied in vitro in Chinese hamster ovary (CHO-KI-BH4) cells in the absence of exogenous metabolic activation systems. CHO-KI-BH4 cells were exposed to 4CMB, 4HMB, or BC for 2 hr. Tests of relative plating efficiency indicated that 4HMB is nontoxic at concentrations up to 100 ug/ml; above 100 ug/ml 4HMB precipitated from soln. 4CMB was slightly more toxic than BC. Sister chromatid exchanges (SCE) were significantly increased by BC in a dose-related manner; the max effect of 4CMB was a doubling of the background frequency of SCE at a concentration of 7 ug 4CMB/ml; 4HMB had no effect on the frequency of SCE. 4CMB produced moderate but significant chromosomal aberrations (CA) within a concentration range of 10-20 ug/ml; BC produced somewhat more CA but at higher doses than 4CMB. 4HMB produced no effect on CA. 4CMB produced a slight increase in the frequency of cell mutations (CM) within a narrow range of doses around 10 ug/ml, BC produced a small increase at a dose of 18 ug/ml, and 4HMB had no effect on CM. Results indicate that 4CMB and BC are weakly mutagenic in the absence of an exogenous metabolic activation system. SCE, CA, and CM test results agreed quantitatively and qualitatively. (4 Refs)

93. AN ASSESSMENT OF THE CLASTOGENIC POTENTIAL OF 4-CHLOROMETHYLBIPHENYL IN HUMAN LYMPHOCYTES IN VITRO.

Richardson CR, Wildgoose J
Central Toxicology Lab., Genetic Toxicology Section, Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire, England
Mutat Res; 100(1-4):287-293 1982

Clastogenicity of 4-chloromethylbiphenyl (4CMB) was studied in vitro in lymphocytes from four human donors. The lymphocytes were stimulated by phytohemagglutinin. 4CMB produced genetic damage in cells from 3/4 donors according to one criterion and in cells from 1/4 donors according to a second criterion. The most common defects produced were chromatid and chromosome gaps. Results indicate that 4CMB is clastogenic but only at concentrations that are cytotoxic. (3 Refs)

94. METAPHASE ANALYSIS OF HUMAN LYMPHOCYTES TREATED WITH 4-CHLOROMETHYLBIPHENYL AND BENZYL CHLORIDE.

Kirkland DJ, Smith KL, Jenkinson PC
Toxicol Lab. Ltd., Bromyard Road, Ledbury, Herefordshire, HR8 1LG, England
Mutat Res; 100(1-4):297-299 1982

Chromosome mutagenicity of 4-chloromethylbiphenyl (4CMB) and benzyl chloride (BC) was assayed in lymphocytes from a healthy human donor. Mitosis was inhibited by 4CMB at concentrations greater than 20 ug/ml and by BC at concentrations greater than 10 ug/ml. At lower concentrations neither compound increased the number of cells showing chromosome breaks or the number of breaks/cell. 4CMB increased gaps at 10 ug/ml. Results indicate that neither 4CMB nor BC is mutagenic in human lymphocytes. (2 Refs)

95. SISTER-CHROMATID EXCHANGES IN HUMAN LYMPHOCYTES TREATED WITH 4-CHLOROMETHYLBIPHENYL AND BENZYL CHLORIDE.

Kirkland DJ, Jenkinson PC, Smith KL
Toxicol Lab. Ltd., Bromyard Road, Ledbury, Herefordshire, HR8 1LG, England
Mutat Res; 100(1-4):301-304 1982

Induction of sister chromatid exchanges (SCE) in human lymphocytes by exposure to noninhibitory doses of 4-chloromethylbiphenyl (4CMB) and benzyl chloride (BC) was studied. 4CMB produced significant increases in frequency of SCE. BC produced increases that were just barely significant. Results suggest that SCE assay may be a more accurate test of mutagenicity in human lymphocytes than chromosome breakage assay. (3 Refs)

96. INVESTIGATION OF THE CYTOGENETIC EFFECTS OF BC AND 4CMB ON HUMAN PERIPHERAL LYMPHOCYTES IN VITRO.

Hartley-Asp B
Pharmacology Dept., AB Leo, Box 941, S-251 09 Helsingborg, Sweden
Mutat Res; 100(1-4):295-296 1982

Cytogenetic effects of 4-chloromethylbiphenyl (4CMB) and benzyl chloride (BC) were studied in cultured lymphocytes derived from the venous blood of a healthy human donor. Neither 4CMB nor BC produced any increase in the frequency of chromosomal aberrations. Cell division was delayed and sister chromatid exchanges increased by 4CMB but not BC. Results indicate that neither 4CMB nor BC is clastogenic in human peripheral blood lymphocytes in vitro. (1 Ref)

97. CYTOGENETIC EFFECTS OF CIGARETTE SMOKE CONDENSATES IN VITRO AND IN VIVO.

Madle S, Korte A, Obe G

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Hum Genet; 59(4):349-352 1981

Cigarette smoke condensates (CSC: 10-100ug/ml) from AB (reference mixture), Virginia, Burley, Orient, and HE (British) cigarettes were compared for the ability to induce sister-chromatid exchanges (SCE) in human lymphocytes in vitro. AB CSC (75, 150, 300 mg/kg) were tested for in vivo SCE induction in Chinese hamster bone marrow cells. SCE induction in lymphocytes was dose-dependent, and no statistical differences were found among the different CSC. By contrast, in vivo experiments showed no elevation of SCE in hamster bone marrow cells; no differences existed between male and female animals. The po administration used in the hamster experiment may have decreased the amount of CSC reaching the bone marrow cells. Experiments with Chinese hamsters cannot effectively simulate the chronic exposure experienced by humans who smoke. (41 Refs)

98. MUTAGENICITY AND CHEMICAL ANALYSIS OF ALIPHATIC AND AROMATIC FRACTIONS OF PRUDHOE BAY CRUDE OIL AND FUEL OIL NO. 2.

Ellenton JA, Hallett DJ

Dept. of the Environment, Wildlife Toxicology Div., Natl. Wildlife Res. Center, Ottawa, Ontario K1A OE7, Canada

J Toxicol Environ Health; 8(5/6):959-972 1981

Chemical analyses of aliphatic and aromatic fractions of Prudhoe Bay crude (PBC) oil and fuel oil number 2 and their potential mutagenicity were investigated. Fraction 1 of both oils exhibited no mutagenic activity. PBC oil fractions 3 and 4 and fuel oil number 2 fraction 4 produced weak mutagenic activity with metabolic activation. A significant increase in sister chromatid exchanges occurred after treatment with various concentrations of fraction 3 and 4 from each oil. These results indicate genetic activity residing in the polycyclic aromatic hydrocarbon containing fractions of the tested oils in both bacteria and mammalian cells. (20 Refs)

99. ABSENCE OF MUTAGENIC AND CLASTOGENIC ACTION OF PINE-TAR RESIN IN THE SALMONELLA/MICROSOMAL AND CHO CULTURE SYSTEMS.

Athanasiou K, Lillis D

Inst. Biological Res., Natl. Hellenic Res. Foundation, 48, Vas. Constantinou Ave., Athens, Greece

Mutat Res; 103(3-6):229-232 1982

Salmonella typhimurium strains TA98 and TA100, with and without S9 mix prepared from livers of rats pretreated with Aroclor 1254, were subjected to doses of 0.1-4 mg/plate of the natural pine tar resin used in Greek 'retsina' wine in the Ames test. Sister-chromatid exchanges, chromatid abnormalities, and mitotic index were determined for Chinese hamster ovary cells (CHO) subjected to doses of 0.025-1 mg/ml of the same resin. Neither test indicated mutagenicity, but mitotic arrest of CHO cells was evident at all concentrations tested. (10 Refs)

100. POTENTIATION OF GENOTOXICITY BY CONCURRENT APPLICATION OF COMPOUNDS FOUND IN BETEL QUID: ARECOLINE, EUGENOL, QUERCETIN, CHLOROGENIC ACID AND MN++.

Stich HF, Stich W, Lam PP
Environmental Carcinogenesis Unit, British Columbia Cancer Res. Centre, 601 West 10th Ave., Vancouver, BC V5Z 1L3, Canada
Mutat Res; 90(4):355-363 1981

Clastogenic activities of five components of betel quid were studied in Chinese hamster ovary (CHO) cells. CHO cell cultures were exposed to the alkaloid arecoline (AR: 50, 100, 200, or 400 ug/ml), eugenol (EU: 50, 100, or 200 ug/ml), chlorogenic acid (CA: 25, 50, 100, or 200 ug/ml), quercetin (QU: 25, 50, or 100 ug/ml), Mn++ (10(-4) M), or combinations of these. The frequency of chromosome aberrations (FCA) in CHO cultures was measured after 3 hr exposure. Combined application of AR and QU produced FCA 2.8-4.6x as high as the sum of the FCA produced by AR or QU alone. Chromatid exchanges accounted for approx 56-74% of all aberrations. AR plus EU and AR plus CA also produced FCA higher than the sum of the FCA produced by individual compounds. The combination of AR, CA, and Mn++ produced FCA higher than the sum of FCA for the individual compounds or combinations of two compounds. When compounds were combined, aberrations were produced by concentrations of CA and EU that alone did not produce aberrations. Results indicate potentiation of clastogenic activity by the presence of more than one clastogenic agent. Distinction should be made between a genotoxic range and a cogenotoxic range of concentrations in the study of genotoxic agents. (51 Refs)

GENERAL REVIEWS

101. RETINOL (VITAMIN A) INHIBITS SISTER CHROMATID EXCHANGES AND CELL CYCLE DELAY INDUCED BY CYCLOPHOSPHAMIDE AND AFLATOXIN B1 IN CHINESE HAMSTER V79 CELLS.

Huang CC, Hsueh JL, Chen HH, Batt TR
Dept. Experimental Biology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Carcinogenesis; 3(1):1-5 1982

Retinol (vitamin A alcohol) at the doses tested neither induced an increase of frequency of sister chromatid exchanges (SCE) nor cell cycle delay in Chinese hamster V79 cells with or without the metabolic activation of S-9 mix. However, it inhibited SCE frequencies and cell cycle delay in V79 cells induced by the indirect mutagen cyclophosphamide or aflatoxin B1. The inhibition was found to be dose an d time dependent. These results suggest that retinol itself may have no direct effect on the genetic materials but rather exert its effects possibly by inhibiting the metabolic activation of an indirect mutagen or carcinogen. Thus, the antitumor activities of retinoids may not be limited to the widely accepted role of the preventing the promotion step but also the initiation step of carcinogenesis. (Author abstract) (33 Refs)

102. DOSE- AND TIME-RESPONSE RELATIONSHIPS OF TRIETHYLENEMELAMINE-INDUCED CHROMOSOMAL ABERRATIONS IN RAT BONE MARROW CELLS.

Levine BS, Pergament E, Driscoll K
Drug Safety Evaluation Div., Ortho Pharmaceutical Corporation, Raritan, NJ, 08869
Toxicol Lett; 10(2):281-285 1982

Variables and optimal conditions necessary for the use of triethylenemelamine (TEM) as a positive control agent in rat cytogenetic assays were studied. TEM-induced chromosome aberrations were observed 6 and 24 hr and to a significantly lesser extent 48 hr after single ip doses of 0.125 to 0.50 mg/kg. Single doses of either 0.25 or 0.50 mg/kg TEM with sampling of bone marrow cells 24 hr after treatment resulted in the greatest yield of chromosomal aberrations. Because 0.50 mg/kg may have been cytotoxic, the 0.25 mg/kg dose level and 24 hr killing apparently represent optimal conditions for using TEM as a positive control agent. (10 Refs)

103. A COMPARISON OF ADRIAMYCIN AND MAMSA IN VITRO: CELL LETHALITY AND SCE STUDIES.

West C, Stratford IJ, Barrass N, Smith E
Radiobiology Unit, Physics Dept., Inst. Cancer Res., Clifton Ave., Sutton, Surrey SM2 5PX, England
Br J Cancer; 44(6):798-809 1981

We have compared the actions of Adriamycin (ADM) and mAMSA in Chinese hamster V79 cells in vitro, using cell survival and sister-chromatid exchange as end-points. Equimolar concentrations of ADM and mAMSA show similar toxicities to exponentially growing cells, and both drugs are less effective in killing chronically hypoxic and plateau-phase cells. Cytotoxicity to thermotolerant cells (41 C for 16 hr previously) shows little difference from that for exponential cells. Pretreating cells with misonidazole under hypoxic conditions reduces the toxicity of both ADM and mAMSA. In addition, an ADM-resistant Chinese hamster cell line, 77A-177, was cross-resistant to mAMSA. Finally, low equimolar sub-toxic doses of both drugs were found to cause similar increases in the levels of sister-chromatid exchanges in V79 cells. These results reveal no major difference in activity between ADM and mAMSA in vitro. (Author abstract) (35 Refs)

104. CYTOTOXICITY OF L-CANAVANINE IN VITRO.

Naha PM
Dept. Cell Biology, Christie Hosp. and Holt Radium Inst., Paterson Labs., Manchester M20 9BX, England
Anticancer Res; 1(5):275-277 1981

Cytostatic cellular reactions caused by L-canavanine (CAN) were studied in BALB/ c-3T3 cells and phytohemagglutinin-stimulated human lymphocytes. BALB/c-3T3 cells were exposed to L-arginine (ARG) or CAN at concentrations of 1 x 10(-4) M, 1 x 10(-5) M, or 5 x 10(-6) M for 48 hr. Human lymphocytes were exposed to CAN at 1 x 10(-4) M to 1 x 10(-6) M for 50 hr at 37 C, then mitotic indices, karyotypes, and sister chromatid exchanges were studied. Of BALB/c-3T3 cells exposed to CAN for 48 hr then placed in growth medium without CAN, 90% treated with up to 1 x 10(-4) M recovered to continue DNA synthesis within 24 hr. Compared with ARG-treated cells, high labeling indices were observed after withdrawal of CAN, probably due to partial synchrony caused by CAN-induced inhibition of DNA synthesis. At lower concentrations (1 x 10(-6) M), the lower labeling index suggested partial inhibition and poorer synchrony. Cells exposed to 1 x 10(-4) M CAN for 48 hr recovered to form colonies as efficiently as untreated controls. In the presence of CAN, however, there was total inhibition of colony-forming ability. In the presence of CAN, few phytohemagglutinin-stimulated lymphocytes proceeded with mitosis, while mitosis continued when CAN (1 x 10(-4) M) was withdrawn. No difference in chromosomal aberrations or sister chromatid exchanges were noted between CAN treated and control cultures. (17 Refs)

105. MUTAGENICITY AND TOXICITY OF FUROCOUMARINS: COMPARATIVE INVESTIGATIONS IN 2 TEST SYSTEMS.

Abel G, Schimmer O
Institut fur Botanik und Pharmazeutische Biologie, Universitat Erlangen-Nurnberg, Schlossgarten 4, D-8520 Erlangen, W. Germany
Mutat Res; 90(4):451-461 1981

Photomutagenicity and phototoxicity of the linear furocoumarins 8-methoxypsoralen (8-MOP) and 8-isoamylenoxypsoralen (8-IOP) and of the angular furocoumarin 5'-methylangelicin (5-MA) were studied. Human peripheral lymphocytes (HPL) were cultured in the presence of 5-bromodeoxyuridine. At 47 hr the cultures were exposed to 8-MOP (21.6 ug/ml), 8-IOP (27.0 ug/ml), or 5-MA (20.0 ug/ml). At 48 hr the cultures were irradiated with UV-A. Cells were examined at 72 hr. 8-MOP and UV or 5-MA and UV produced significant increases in the frequency of sister chromatid exchanges (SCE) compared with controls. 8-MOP had the greatest effect, increasing SCE by a factor of 2. 8-IOP had no effect. 5-MA produced irregular results. Cultures of an arginine-dependent strain of Chlamydomonas reinhardii were exposed to the test compounds and immediately irradiated with UV-A. Equimolar concentrations of 8-MOP and 5-MA produced equal levels of toxicity. 8-IOP produced much less toxicity in a longer time period. 8-MOP produced the greatest mutation rate, as indicated by induction of Arg+ revertants. 8-IOP produced similar mutation rates but required 3x the UV-irradiation time. 5-MA was much less mutagenic. Results indicate that monofunctional furocoumarins present a smaller mutagenic hazard than bifunctional furocoumarins and should be preferentially tested for therapeutic efficiency. (26 Refs)

106. CELL TRANSFORMATION, MUTATION, AND CANCER.

Barrett JC
Environmental Carcinogenesis Group, Natl. Inst. Environmental Health Sciences, Lab. Pulmonary Function and Toxicology, NC, 27709
Gann Monogr Cancer Res; 27:195-206 1982

The abilities of 2-aminopurine (AP) and diethylstilbestrol (DES) to induce neoplastic transformation and/or somatic mutation in Syrian hamster embryo cell assays was investigated. AP is a well-defined mutagen and an inactive carcinogen, while DES is a known carcinogen and is inactive as a mutagen. AP was shown to be, at best, a weak transforming agent. DES failed to induce measurable somatic mutations at either of the two loci tested. At the chromosome level, a mutation is one cause of morphological transformation and possibly cancer. Chromosome changes are very early manifestations of a neoplastic alteration and may be an initial part of neoplastic development in vivo. A theory on the relationship between tumor initiation, differentiation, and chromosome mutations is proposed. The carcinogen induces chromosome mutations, gene mutations, and nonmutational changes, any of which might lead to neoplastic development. The most frequent event results from a chromosome mutation which prevents normal cellular differentiation, thereby providing a selective growth advantage for the altered cells. The altered cell grows and mutational or nonmutational secondary changes may occur. (63 Refs)

107. SISTER CHROMATID EXCHANGES AND MUTAGENIC CARCINOGENS.

Wolff S
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Gann Monogr Cancer Res; 27:109-124 1982

Use of sister chromatid exchange (SCE) induction for detecting mutagenic effects in mammalian cells is reported. SCEs are produced with unrepaired lesions are present when the cell passed through S phase and chromosome replicated. Some chemical mutagens caused a 10-fold increase in background level of SCEs at concentrations of the chemical less than 1/100th of that required to induce ordinary chromosomal aberrations. Cultured Chinese hamster ovary cells with rat liver microsomes can be used to detect SCE induction. Suspected mutagens can be prescreened with the SCE test in sensitive mammalian cells by treating the cells in vitro with and without S-9 mix. Negative compounds should be tested in an in vivo test system to determine if the compounds can be activated under in vivo conditions. The SCE test was used to determine the following: which benzene metabolites were most likely responsible for the biologic effects, the stage of embryogenesis at which cells that are genetically capable of producing aryl hydrocarbon hydroxylase activated promutagens or procarcinogens, how long lesions induced by a short-lived proximate carcinogen last in cells of differing repair capacity, and whether mammalian cells exhibit novel DNA repair mechanisms. (58 Refs)

108. ROLE OF DNA REPAIR IN MUTAGENESIS OF CHINESE HAMSTER OVARY CELLS BY 7-BROMOMETHYLBENZ[A]ANTHRACENE.

Thompson LH, Brookman KW, Carrano AV, Dillehay LE
Biomedical Sciences Div., L-452, Lawrence Livermore Natl. Lab., P.O. Box 5507, Livermore, CA, 94550
Proc Natl Acad Sci USA; 79(2):534-538 1982

The role of DNA repair in mutagenesis was studied in normal, repair-proficient Chinese hamster ovary cells and in two mutant strains that are deficient in excision repair. By using the mutagen 7-bromomethylbenz[a]anthracene (7-BrMeBA) and the technique of alkaline elution of DNA, the mutants were found to be defective at or before the incision step of excision repair. Dose-responses were determined for cell killing, mutation induction at three loci, and sister chromatid exchanges over a survival range of 1.0-0.1 after 7-BrMeBA treatment. The mutants were five-fold more sensitive to killing than were the normal cells, but the degree of hypersensitivity to mutation induction varied depending on the mutant strain, the genetic marker, and the dose of mutagen. In each instance, the dose-response curve for mutations was essentially linear in the repair-deficient cells. In the normal cells, however, the curves for induced resistance to thioguanine and azaadenine were complex and were curvilinear with increasing slope at low doses. This behavior may be attributable to saturation of the excision repair system. No difference was seen in the efficiency of inducing ouabain-resistant mutations in the repair-deficient cells compared to the normal cells, indicating a qualitatively different behavior of this marker. These results are consistent with excision repair of 7-BrMeBA damage being error-free in Chinese hamster ovary cells. Sister chromatid exchange, another manifestation of DNA damage, also was induced with greater efficiency in the repair-deficient cells. (Author abstract) (34 Refs)

109. HARMAN AND NORHARMAN: INDUCTION OF SISTER-CHROMATID EXCHANGES IN HUMAN PERIPHERAL LYMPHOCYTES IN VITRO AND INTERACTION WITH ISOLATED DNA.

Madle E, Obe C., Hansen J, Ristow H
Institut fur Genetik, Freie Universitat Berlin, Arnimallee 5-7, D-1000 Berlin 33, W. Germany
Mutat Res; 90(4):433-442 1981

The effects of harman, norharman, and derivatives of both compounds on human peripheral lymphocytes (HPL) in vitro and isolated DNA from calf thymus were studied. The frequency of sister chromatid exchanges in HPL was increased by harman or harman-derivatives but not by norharman or norharman-derivatives. Transcription of isolated DNA was inhibited by harman and to a lesser extent by norharman. In a filter binding assay harman bound DNA more strongly than norharman. (20 Refs)

110. SISTER-CHROMATID EXCHANGE IN PATIENTS WITH HEPATITIS.

Ghosh PK
Dept. Anthropology, Univ. Delhi, Delhi-110 007, India
Mutat Res; 103(3-6):303-306 1982

The lymphocytes of 28 adult patients, 12 of whom had virus 'A' and 16 of whom had virus 'B' hepatitis as determined by serum antigen tests, were examined for sister-chromatid exchanges (SCEs) induced by bromodeoxyuridine (10 ug/ml). Patients with virus 'A' hepatitis had a mean SCE/cell of 8.61 +-2.21, those with virus 'B' had a mean SCE/cell of 10.12 +-2.83; 20 control patients' lymphocytes averaged 5.21 +-1.26 SCE/cell. After complete chemical and biochemical recovery, 2/6 of the virus 'A' hepatitis patients and 1/5 of the virus 'B' hepatitis patients had reduced SCEs, although not to levels equivalent to controls. Failure of SCE levels to return to control levels may have been due to the presence of the not replaced virally-affected lymphocytes still in the system after the patients had recovered. (17 Refs)

111. ALTERATIONS IN THE FREQUENCY OF SISTER CHROMATID EXCHANGES IN FLATFISH FROM PUGET SOUND, WASHINGTON, FOLLOWING EXPERIMENTAL AND NATURAL EXPOSURE TO MUTAGENIC CHEMICALS.

Stromberg PT, Landolt ML, Kocan RM
Office Marine Pollution Assessment, Natl. Oceanic and Atmospheric Admin., Boulder, CO
Alterations in the Frequency of Sister Chromatid Exchanges in Flatfish from Puget Sound, Washington, Following Experimental and Natural Exposure to Mutagenic Chemicals. Available from National Technical Information Service, Springfield, VA, as PB82-124637:, 53 pp., 1981.

Contamination of the aquatic environment by chemical pollutants has become a serious environmental problem which is heightened by the fact that a number of these contaminants have been demonstrated to be mutagenic or carcinogenic. In the present study the technique of sister chromatid exchanges (SCE) was applied to English sole (Parophrys vetulus) collected from Puget Sound, Washington. SCE were observed 5.5 days after in vivo exposure to a thymidine analogue, bromodeoxyuridine which allows for differentiation in the staining affinity of chromatids and visualization of exchanges between them. To test the efficacy of this technique as a useful tool in screening fish for evidence of exposure to mutagenic chemicals, the chromosomes of English sole from a polluted site were examined and found to have a significantly higher SCE rate than in the baseline. This study showed that the technique of SCE could be successfully applied to a marine fish species and that the effects of low concentrations of mutagens could be detected using this method. (Author abstract)

112. CYTOGENETIC EFFECTS ON THE EASTERN MUD MINNOW, UMBRA PYGMAEA, EXPOSED TO ETHYL METHANESULFONATE, BENZO[A]PYRENE, AND RIVER WATER.

Hooftman RN, Vink GJ
Organization for Industrial Res., TNO, P.O. Box 217, 2600 AE delft, Shoemakerstr aat 97, The Netherlands
Ecotoxicol Environ Saf; 5(3):261-269 1981

The eastern minnow, Umbra pygmaea, was exposed to two known genotoxic agents and to water from the Rhine river at Lobith, The Netherlands. Both chromosome aberrations and sister chromatid exchanges (SCE) were scored. Fish were exposed to 0, 8, 40, and 200 mg ethylmethanesulfonate (EMS)/liter and 0, 10(-5), and 10(-4) mg benzo[a]pyrene (BaP)/liter at 20 C for 48 hr. Two additional groups of fish were exposed to 10(-4) mg/liter BaP for 4 and 6 days. EMS induced chromatid breaks, chromosome breaks, and gaps in gill and fin tissue; most of the aberrations were chromatid aberrations. EMS concentrations of 8, 40, and 200 mg/liter induced 1.1, 6.8, and 19.6% metaphases with aberrations, respectively. BaP only induced chromosome aberrations in fish exposed to the higher concentration; both chromatid breaks and gaps were seen. Activity of benzo[a]pyrene hydroxylase was near the detection limit (0.01 umole/g liver/hr). Bromodeoxyuridine injection to improve the number of metaphases with differential staining gave best results in gill tissue after two or three injections. Rhine water induced chromosome aberrations (chromatid breaks, chromosome breaks, gaps) and increased the number of SCE/metaphase. U pygmaea was suitable for detecting cytogenetic effects of chemical pollution in the aquatic environment. (18 Refs)

113. THE KILLIFISH NOTHOBRANCHIUS RACHOWI, A NEW ANIMAL IN GENETIC TOXICOLOGY.

van der Hoeven JC, Bruggeman IM, Alink GM, Koeman JH
Dept. Toxicology, Agricultural Univ., De Dreijen 12, Wageningen, The Netherlands
Mutat Res; 97(1):35-42 1982

The use of Nothobranchius rachowi (Cyprinodontidae) in a sister-chromatid exchange (SCE) test is described and compared with SCE results obtained with Umbra pygmaea. N rachowi was treated with 5-bromo-2'-deoxyuridine (BrdU) by placing 150 mg/liter of the compound directly into the tap water in the aquarium; U pygmaea received BrdU injections (0.5 mg/g ip). Gill tissue cell suspensions from both fish were examined for SCE following 70 hr exposure to ethylmethane sulfonate (EMS: 24-120 ug/ml) in the aquarium water, and N rachowi was also exposed for 50 hr in a similar fashion to cyclophosphamide (CP: 2.5-50.0 ug/ml). Both fish showed concentration-dependent SCE responses to EMS; N rachowi exhibited dose-dependent response to CP, which indicated that CP was almost 3x as effective an inducer of SCEs as EMS. Advantages of N rachowi over U pygmaea in SCE tests include possible larger number of metaphases per specimen, more rapid testing, potential for laboratory rearing of fish, and 16 vs

22 chromosomes. A disadvantage of N rachowi is its requirement for warmer water (25-27 C vs 20 C). (10 Refs)

114. OXYGEN DEPENDENCE OF SISTER-CHROMATID EXCHANGES.

Gutierrez C, Lopez-Saez JF
Instituto de Biologia Celular, Velazquez 144, Madrid-6, Spain
Mutat Res; 103(3-6):295-302 1982

Root meristems of Allium cepa L were subjected to gas mixtures of 5, 10, 20, and 100% oxygen pressure to observe the effect of oxygen on subsequent 5-bromodeoxyuridine (BrdUrd)-induced sister-chromatid exchanges. Onion roots previously grown at a fixed oxygen pressure were allosed to replicate in the presence of BrdUrd for either one or two cycles. SCE frequencies were unchanged at oxygen pressure of 20% (air) or below, but increased at higher levels. The mechanism responsible for BrdUrd-induced SCE formation appears to operate by exchanging postreplicative DNA portions, with activation of newly incorporated BrdUrd in the formation of SCEs. (20 Refs)

115. MEASUREMENT OF SCE FREQUENCIES IN PLANTS: A SIMPLE FEULGEN-STAINING PROCEDURE FOR VICIA FABA.

Tempelaar MJ, De Both MTJ, Versteegh JEG
Dept. Genetics, Biology Center, Univ. Groningen, P.O. Box 14, 9750 AA Haven, The Netherlands
Mutat Res; 103(3-6):321-326 1982

A Feulgen staining procedure for observing sister-chromatid exchange (SCE) frequencies in bean roots after 5-bromodeoxyuridine (BrdU) incorporation is described in which extended HCl hydrolysis of DNA is utilized to obtain differential contrast. Chromosomes with incorporated BrdU resist depolymerization when hydrolysis time is extended from 15-40 min, depending on the bean variety, and the result is clearer staining. Contrast is increased by using higher concentrations of BrdU, and 5-fluorodeoxyuridine and uridine may be omitted, although the rate of spontaneous SCE increases. (7 Refs)

116. ASPERGILLUS NIDULANS AS A TEST ORGANISM FOR CHEMICAL MUTAGENS.

Igwe CN, Cohn P
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Mutat Res; 100(1-4):127-131 1982

Effects of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) on survival, mitotic segregation, mitotic gene conversion, and point mutations in three strains of Aspergillus nidulans were studied. BC had the greatest effect and 4HMB the least on survival and gene conversion in a diploid strain and point mutation in a haploid strain. Neither 4CMB, 4HMB, nor BC had any effect on mitotic segregation. (4 Refs)

117. TESTING FOR MITOTIC CROSSING-OVER AND INDUCED ANEUPLOIDY USING ASPERGILLUS NIDULANS AS PART OF THE UKEMS TEST PROGRAMME.

Watkins P
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Mutat Res; 100(1-4):133-138 1982

Abilities of 4-chloromethylbiphenyl (4CMB), benzyl chloride (BC), and 4-hydroxymethylbiphenyl (4HMB) to induce mitotic crossing-over in a diploid strain of Aspergillus nidulans (strain P), heterozygous for the gene determining resistance to p-fluorophenylalanine, were studied in selective media. 4CMB gave clear indication of the induction of crossing-over with increases over the length of the pre-incubation period. Inclusion of S9 mix reduced the effect. BC produced a small induction of crossing-over clearly noticeable only when the conidia were treated after 5 and 6 hr of incubation. 4HMB did not show any positive response in the assay. (4 Refs)

118. RECENT ADVANCES IN CANCER CYTOGENETICS.

Pogosiants EE
All-Union Cancer Res. Center, Moscow, USSR
Genetika; 17(12):2087-2099 1981

Recent studies in the field of cancer cytogenetics are reviewed with special emphasis on karyotypic changes in leukemia and carcinoma cells, prezygotic chromosome mutations specific for certain human tumors, and phenomena of gene amplification characteristic for a number of tumors and for cells resistant to antineoplastic agents. Specific karyotypic changes were observed in human and murine leukemias, as well as in a number of experimental sarcomas and carcinomas. Specific involvement of chromosome 15 was recorded in murine radiation-induced and carcinogen-induced T-cell leukemias; also, trisomy for chromosome 15 or translocation involving chromosome 15 were detected in B-cell leukemias and lymphomas. Specific involvement of the distal third of chromosome 15 indicated that this region contains the cluster of genes responsible for normal differentiation and malignant transformation of lymphoreticular cells. Specific prezygotic chromosome aberrations were observed in retinoblastoma (deletion in the long arm of chromosome 13), nephroblastoma (deletion in the short arm of chromosome 11), and in familial kidney carcinoma (translocation between chromosomes 3 and 8). Specific resistance of eukaryotic cells to methotrexate was shown to be associated with the presence of homogenously stained regions and the number of double microchromosomes. (73 Refs) (In RUS)

119. THE LEUKEMIC CELL.

Catovsky D
MRC Leukaemia Unit, Royal Postgraduate Medical Sch., London, England
Methods Hematol 2: 281 pp., 1981.

New objective criteria for diagnosis and classification of leukemia have permitted better characterization of various forms of leukemia, facilitated recognition of new disease entities, contributed to understanding of the natural history of leukemia, and led to improved management of the disease. Rapid advances in technology have allowed better description of cellular events in hemopoietic malignancies while making it more difficult for specialists to keep up with new developments. Techniques currently available for the study of leukemic cells are presented in sufficient detail to make the techniques of practical value. A general review is presented. Individual topics discussed include cytochemistry in classification of leukemias, bone marrow histology, ultrastructure of the leukemic cell, membrane markers in leukemia, chromosomes in leukemia and lymphoma (with emphasis on methodology), terminal transferase, the clonal culture in vitro of leukemic cells, and glucocorticoid receptors. Discussion includes methods, clinical and scientific principles, and the significance of results. Problems that may be encountered are described and methods of resolution presented. (892 Refs)

120. OVERVIEW: THE LEUKEMIC CELL.

Catovsky D

MRC Leukemia Unit, Royal Postgraduate Medical Sch., London, England

Methods Hematol; 2:1-28 1981

Leukemias are classified generally as acute or chronic and myeloid or lymphoid. Within the broad categories are many individual disease entities that differ in prognosis and response to therapy. Recognition of specific forms requires consideration of morphology, cytochemistry, histology, membrane markers, enzyme assays, chromosome analysis, cloning of individual cell lines, and glucocorticoid receptors. (171 Refs)

121. CHROMOSOMES IN LEUKEMIA AND LYMPHOMA WITH SPECIAL EMPHASIS ON METHODOLOGY.

Testa JR, Rowley JD

Cytogenetics Lab., Section Hematology and Oncology, Dept. Medicine, Univ. Chicago, Chicago, IL

Methods Hematol; 2:184-202 1981

Methodology of chromosome analysis in diagnosis of leukemia is presented. Cells for study may be cultured from cells from bone marrow aspirate, bone core biopsy, peripheral blood, lymph nodes, spleen, or effusions. Specimens may be stained by conventional, quinacrine-banding, Giemsa-banding, reverse-banding, or C-banding techniques. Chromosome abnormalities of chronic myeloid leukemia, acute leukemia, malignant lymphoma, and multiple myeloma are summarized. (48 Refs)

122. THE NATURE OF CHROMOSOME BANDS AND THEIR SIGNIFICANCE FOR CANCER RESEARCH.

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Clinical and Population Cytogenetics Unit, Western General Hosp., Edinburgh EH4 2XU, Scotland

Anticancer Res; 1(4):205-215 1981

Chromosome bands are discussed with respect to classification, properties, banding techniques, and their significance to cancer research. The two main classes of chromosome bands are constant, heterochromatic bands (CHB) and fluctuant bands (FB), with kinetochores and nucleolar organizers recognized as separate classes. CHB have been associated with regions containing satellite DNA in many species. FB correspond to pachytene chromomeres, and may represent the condensation process occurring in mitotic chromosomes. Banding patterns are used to identify whole or parts of chromosomes, gene mapping, and to study the clinical significance of polymorphisms of CHB. Banding techniques revealed the presence of the Philadelphia chromosome in most cases of chronic myeloid leukemia; few, if any, other cancers show such a clear correlation with a specific chromosomal abnormality. Banding techniques have revealed that cancers tend to be associated with particular chromosome abnormalities and that certain chromosomes tend to be altered in cancerous cells. Burkitt's lymphoma retinoblastoma, and Wilm's tumor are each associated with specific chromosome abnormalities. The presence of 'homogenously staining regions' and double minute chromosomes in some tumor cells is discussed. While chromosome changes in cancer cells can be identified by banding techniques, the significance of such changes is unclear. (131 Refs)

123. PROCANCER CLASS OF GENES AND GENERATION OF CHROMOSOME MUTATION.

Sasaki MS, Ejima Y

Radiation Biology Center, Kyoto Univ., Yoshida-konecho, Sakyo-ku, Kyoto 606, Japan

Gann Monogr Cancer Res; 27:85-94 1982

The nature of inherent mutation associated with chromosome instability and high cancer risks is discussed. Human genetic syndromes associated with chromosome instability include Fanconi's anemia (FA), ataxia telangiectasia (AT), Bloom's syndrome (BS), incontinentia pigmenti (IP), and, perhaps xeroderma pigmentosum (XP). Chromosome aberrations are primarily of the chromatid type, indicating that the chromosome mutations in these diseases arise in connection with DNA replication. FA, AT, and IP have a significantly high frequency of chromosome aberrations, while the other diseases show normal aberration rates. DNA damage left unrepaired in AT and FA cells might not be subject to repair by post-replication error-prone repair mechanisms or such a mechanism might not operate in these cells. Genetically-determined cancer proneness appears to be caused by an intrinsic sensitivity of instability to chromosome mutation; gross chromosomal change is a prime importance in mutation toward cancer. Certain types of procancer genes with dominant traits express a mutator function and promote chromosome recombination in their somatic cells. Such mutations of de novo origin occur in familial polyposis coli, Gardner's syndrome, Peutz-Jegher's syndrome, nevoid basal cell carcinoid syndrome, hereditary retinoblastoma, dominantly-inherited familial leukemia, and familial colon cancer. The nature of germinal mutations responsible for organ-specific cancer proneness is discussed. (37 Refs)

124. THE USE OF MAMMALIAN CELL MUTANTS TO STUDY THE MECHANISMS OF CARCINOGENESIS.

Trosko JE, Chang CC, Warren ST, Liu PK, Wade MH, Tsushimoto G

Dept. Pediatrics and Human Development, Michigan State Univ., Coll. Human Medicine, East Lansing, MI, 48824

Gann Monogr Cancer Res; 27:159-179 1982

Use of mammalian cell mutants to study the mechanisms of carcinogenesis is reviewed. A genetic approach was used to study molecular mechanisms of initiation and promotion. It was shown that different mutagens induce different types of mutations and that phenotypic expression is influenced by tumor promoters or antipromoters, while mutation fixation is not. General considerations of in vitro mutagenesis at the gene level are discussed. Study of mutagen-sensitive DNA-repair deficient mutants and xeroderma pigmentosum and Bloom's syndrome cells demonstrated that a defect in DNA repair or DNA replication may cause mutagenesis. An in vitro assay to detect tumor promoters was designed with the basic premise that all tumor promoters block metabolic cooperation. Inhibition of cell-cell communication by known tumor promoters might be one of the initial events triggered by tumor promoters. It is possible to study the mechanism of tumor promoters and to screen for environmental promoters. An hypothesis for the relationship of metabolic cooperation and carcinogenesis is proposed. (144 Refs)

125. THE CLINICAL RELEVANCE OF IN VITRO MARKERS.

Jones LW, Kaighn ME
(c/o Kaighn), Pasadena Foundation for Medical Res., 99 North El Molino Ave., Pasadena, CA, 91101
Prostate; 2(2):219-224 1981

The clinical relevance of in vitro markers to prostatic cancer is reviewed with particular reference to prostatic acid phosphatase (Paph). The role of Paph in screening, staging and treatment is discussed. Non-phosphatase antigens, chromosomes, steroid metabolites, and growth control are other marker systems that may have direct clinical relevance for screening, staging, and treatment of prostatic cancer. (21 Refs)

126. BIOLOGICAL MONITORING IN THE IDENTIFICATION OF THE CANCER RISK OF INDIVIDUALS EXPOSED TO CHEMICAL CARCINOGENS.

Vainio H, Sorsa M, Rantanen J, Hemminki K, Aitio A
Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Scand J Work Environ Health; 7(4):241-251 1981

Currently available theoretical and practical possibilities for measuring exposures to chemicals that cause genetic damage (genotoxic agents) and their early effects on the human body are discussed. Few substances suspected to involve the risk of cancer are analyzed routinely from biological samples. Such biological monitoring requires measurable amounts of the chemical or its metabolites. Methods for determination of mutagenicity in biological fluids are reviewed, as are those for determination of products of protein and nucleic acid alkylation. Measurement of early effects of genotoxic agents involves determination of oncodevelopmental proteins, use of clastogenic effects as a measure of early cytogenetic response, analysis of sister chromatid exchanges, and study of morphology of sperm. Available possibilities to evaluate individual risk to genotoxins are still meager. Increases in urinary thioether and mutagenicity can serve as signals which indicate that exposure to electrophilic and mutagenic substances has occurred. Automation of chromosome analysis would mean a major breakthrough in biological monitoring of genotoxins. At present exposure to genotoxins should be monitored by traditional analytical methods and, where not available, the mutagenicity of urine. On some occasions, mutagenicity of urine may prove to be superior to chemical analysis. The course of action to be taken in cases of positive findings is discussed. (63 Refs)

127. GENETIC ASPECTS OF DNA REPAIR DEFICIENCY.

Takebe H, Ishizaki K, Yagi T
Radiation Biology Center, Kyoto Univ., Yoshida-konecho, Sakyo-ku, Kyoto 606, Japan
Gann Monogr Cancer Res; 27:13-19 1982

DNA repair in human cells, specifically those of persons with xeroderma pigmentosum (XP), is reviewed. A survey of the relative levels of unscheduled DNA synthesis (UDS) in XP patients in Japan revealed a unique XP group, group F, in which patients have mild symptoms despite their apparently low repair capacities. In this group, UDS may not represent the actual capacity for excision repair; the resynthesis step was slower than in normal cells and UDS measured during the first few hr after UV irradiation detected only a small portion of the total repair. Inactivation of colony-forming ability and UDS did not correspond in Bloom's syndrome cells treated with mitomycin C and XP strains did not demonstrate high sensitivity to antipain. The presence of UDS suggests the presence of DNA damage subject to some type of repair, but is not proof. The frequency of the population at genetically high risk of cancer in Japan is reported for XP, ataxia telangiectasia, Bloom's syndrome, Fanconi's anemia, retinoblastoma, familial polyposis coli, and Down's syndrome. Overall, the frequency of the population with a high risk of cancer may be 3%. The genetic factor should not be considered a major cause of cancer in Japan. (16 Refs)

128. SENSITIVITY OF VARIOUS GERM-CELL STAGES TO ENVIRONMENTAL MUTAGENS.

Lyon MF
(c/o P. H. Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(3):323-345 1981

Gametogenesis is reviewed with respect to the duration of the various stages and their characteristics in terms of metabolism, chromosomal condensation, and the presence or absence of repair systems. Sensitivity of germ cell stages to mutagens is tested by dominant lethal tests, induction of specific-locus mutations, and translocations. In both males and females chemicals vary in the pattern of effects. While germ cells and their precursors are susceptible to mutagenesis at all stages, including embryonic and fetal stages, sensitivity may differ from that in the adult. Some mutagens affect certain germ-cell stages preferentially. Whether postspermatogonial rather than spermatogonial stages are affected is significant for estimating hazards of environmental mutagens. When exposure is occasional rather than continuous, the genetic hazards may be eliminated by avoidance of conception for a few mo after exposure. Although little is known about effects of chemicals on oocytes, hazards to females cannot be ignored. Rapidly dividing stages of embryonic or immature gonads may be more sensitive to certain mutagens. Effects of age on nondisjunction and on mutation rates are discussed. Germ cells of older persons may be more sensitive to the induction of both mutations and nondisjunction than those of younger persons. (122 Refs)

129. UKEMS COLLABORATIVE GENOTOXICITY TRIAL: CYTOGENETIC TESTS OF 4CMB, BC AND 4HMB: SUMMARY AND APPRAISAL.

Scott D
Paterson Lab., Christie Hosp., Manchester M20 9BX, England
Mutat Res; 100(1-4):313-331 1982

Studies of the genotoxic potential of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) in vitro and of 4CMB in vivo are reviewed. Trials used eight different systems (cultured rat-liver epithelial cells, Chinese hamster V79 and bone marrow cells, human lymphocytes and fibroblasts, and mouse bone marrow cells in vitro, and mouse spermatocytes and oocytes in vivo). Aberrations in chromosomal structure (CA) and sister chromatid exchanges (SCE) were produced by 4CMB and BC but not 4HMB. No consistent differences in effectiveness were found between 4CMB and BC. Changes in chromosome number were not produced by any of the test compounds. 4CMB produced greater increases in CA and SCE in the presence of metabolic activation systems (in rat liver epithelial cells or in the presence of S9 mix) than in the absence of such systems. Since 4CMB does not require activation, the findings suggest that under certain conditions 4CMB can be converted to a more potent electrophile. Overall results indicate that 4CMB is a weak mutagen. (16 Refs)

130. THE GENETIC TOXICOLOGY OF 4-CHLOROMETHYLBIPHENYL (4CMB), 4-HYDROXYMETHYLBIPHENYL (4HMB), AND BENZYL CHLORIDE (BC) AS ASSESSED BY THE UKEMS GENOTOXICITY TRIAL (1981).

Parry JM
Dept. Genetics, Univ. Coll. Swansea, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):411-416 1982

Studies of the genetic toxicology of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethybiphenyl (4HMB), and benzyl choride (BC) are reviewed. Bacterial studies showed that 4CMB is a strong, direct-acting mutagen. 4CMB produces frame-shift and base-pair mutations, apparently by different mechanisms. In fungi 4CMB produced point mutations, mitotic gene conversions, primary DNA damage, and mitotic crossing-over; the presence of metabolic activation systems (MAS) reduced overall toxicity without affecting genetic effects of 4CMB. In mammalian cell cultures 4CMB produced repairable DNA damage, point mutations, chromosome aberrations, and sister chromatid exchanges. In vivo studies did not show that 4CMB induces dominant lethal mutations, micronuclei, aberrations of sperm morphology, or skin tumors. Initial findings suggest that 4CMB may be a weak skin carcinogen. Bacterial studies showed BC to be mutagenic with approx 10% of the base-pair substitution activity of 4CMB. The mutagenic activity of BC increased in the presence of MAS. In fungi BC had mutagenic activity similar to 4CMB. In mammalian cell cultures BC had approx 20% of the activity of 4CMB. No evidence of skin carcinogenicity has been found after 10 mo. No evidence for mutagenicity of 4HMB was found in any system tested. Overall results indicate the value of a range of tests in determining genetic toxicology of compounds. (8 Refs)

131. AN EVALUATION OF THE GENETIC TOXICITY OF EPICHLORHYDRIN. A REPORT OF AN EXPERT GROUP OF THE INTERNATIONAL COMMISSION FOR PROTECTION AGAINST ENVIRONMENTAL MUTAGENS AND CARCINOGENS.

Sram RJ, Tomatis L, Bridges BA, Clemmesen J
(c/o Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(3):299-319 1981

Genetic toxicity of epichlorhydrin (ECH) is reviewed. ECH produces gene mutations in various submammalian species, in mice, cultured mouse lymphoma cells, and in a Syrian hamster transplacental mutagenicity assay. Chromosomal damage has been reported in Vicia faba, human peripheral lymphocytes in vitro, rodent bone marrow, germ cells of mice, and in human peripheral lymphocytes and body fluids. ECH produces repairable DNA damage characteristic of an alkylating agent. The International Collaborative Program on Short-term Tests for Carcinogenicity reported that ECH was mutagenic in the in vitro systems, did not induce sex-linked recessive lethal mutations in Drosophila, and induced sister-chromatid exchanges in mammals. Application of ECH to the skin of rats and mice failed to produce tumors. Administration of ECH sc and im (but not ip) to mice produced local sarcomas and adenomas, although results were inconclusive in one study. Inhalation of 100 ppm (but not 10 ppm) of ECH for 30 days in rats induced squamous cell carcinomas in the nasal cavity. Epidemiologic studies of workers exposed to ECH provided no evidence of a carcinogenic effect; no nasal tumors were observed and the increase in lung cancers found could have been attributed to heavy cigarette consumption. Suggestions for further studies are made. (84 Refs)

132. ASPERGILLUS NIDULANS: SYSTEMS AND RESULTS OF TESTS FOR CHEMICAL INDUCTION OF MITOTIC SEGREGATION AND MUTATION. I. DIPLOID AND DUPLICATION ASSAY SYSTEMS. A REPORT OF THE U. S. EPA GENE-TOX PROGRAM.

Kafer E, Scott BR, Dorn GL, Stafford R
Dept. Biology, McGill Univ., 1205 Ave. Docteur Penfield, Montreal H3A 1B1, Canada
Mutat Res; 98(1):1-48 1982

A critical summary of the 1965-1978 literature is made and background information on the test fungus is presented which covered a wider time period. Most of the reported test systems measured frequency of homo- or hemizygous segregants in heterozygous diploids. These could detect non-mutation genetic damage effects on spindles as well as a variety of types of mutations. However, the different procedures involved made for noncomparable results with the same chemical. Another test system measured increases in frequency of recessive lethals, or effects on recovery of haploid second-order segregants; it was similar to known tests in Drosophila. A third system measured effects on frequency of haploid sectors from duplication strains; it was limited by the availability of a single useful duplication strain. Results on 71 chemicals, including some antineoplastic agents and fungicides, were tabulated. Results of the more elaborate test systems pointed towards the appropriate mammalian system for higher level evaluation. More chemicals need to be tested to fully evaluate the utility of these three basic systems, and more experimental detail is needed on others. Emphasis was put on future use of positive and/or negative controls, full disclosure of results and procedures, use of more than one dose and/or adequate sample size, and proper statistical treatment. (97 Refs)

OTHER RELATED STUDIES

133. ALTERNATIVES TO DONOR MATCHING FOR CONTROL OF GRAFT-VERSUS-HOST DISEASE.

Vriesendorp HM, Klapwijk WM, Visser TP, Zurcher C, Van Bekkum DW
Northwestern Univ. Cancer Center, 701 N. Fairbanks Court, Chicago, IL, 60611
Immunogenetics; 15(1):79-94 1982

Graft-vs-host disease (GvHD) after bone-marrow transplantation in dogs is controlled by many different genetic systems. In littermate combinations identical for the major histocompatibility complex (MHC) the number of systems that influence GvHD is related to the number of donor lymphocytes injected. If the number of donor lymphocytes administered is sufficiently low, minor histocompatibility systems do not influence survival after bone-marrow transplantation. With increasing numbers of donor lymphocytes the beneficial influence of MHC matching on GvHD incidence and severity disappears and minor histocompatibility antigens, coded for on at least two other autosomal chromosomes as well as possibly the Y chromosome, can cause severe GvHD. Female donors appear to cause severe GvHD more frequently than males. In contrast to rhesus monkey and human bone-marrow cells, dog bone-marrow cells are negative in PHA tests. This is in accordance with the generally benign course of GvHD in dogs that are treated with bone-marrow cells only from histocompatible littermate donors. The influence of the sex of the bone-marrow donor on GvHD incidence and severity is not reflected in differences between PHA tests with male and female dog lymphocytes. A better predictive test for GvHD potential than the PHA test appears to be needed. Alternatives to additional donor selection for the prevention of GvHD in histocompatible recipients appear to be the use of a male donor and the removal of lymphocytes from bone-marrow-cell suspensions prior to transplantation. (40 Refs)

134. HOST-MEDIATED MUTAGENESIS FOR DETECTION OF MUTAGENS/CARCINOGENS.

Inui N, Nishi Y
Section Cell Biology and Cytogenetics, Biological Res. Center, Japan Tobacco and Salt Public Corporation, Nakogi 23, Hatano, Kanagawa 257, Japan
Gann Monogr Cancer Res; 27:73-84 1982

An in vivo-in vitro combination assay, host-mediated transplacental mutation assay (HTMA), has been established in which somatic cell mutations can be detected and measured quantitatively. Two genetic markers, 8-azaguanine resistance (8AGr) and 6-thioguanine resistance, were used for detection of forward mutations in fibroblasts of Syrian hamster embryos in pregnant mothers. Mutation frequencies increased linearly with increases in the dose of furylfuramide up to 100 mg/kg body wt of the mothers, when given ip or po; higher mutagenicity was observed following po administration than after ip treatment. Data obtained by HTMA on the effects of coadministration of secondary amines and nitrite, which result in formation of nitrosamines, are presented. Administration of morpholine plus sodium nitrite (500 mg/kg, each) markedly enhanced the mutagenic effect. Coadministration of aminopyrine and sodium nitrite had a more mutagenic effect on hamster embryonic cells than single administration of either compound alone. Thus, N-nitroso compounds produced in the body do cause gene mutations in embryonic tissues and organs. The induction of 8AGr mutations was studied in cultured cells from various organs of embryos of pregnant hamsters treated with benzopyrene (BP), nitrosodimethylamine (DMN), and N-nitrosoethylurea (NMU). Treatment with BP at 200 mg/kg produced more 8AGr mutations in embryonic lung cells than in kidney, liver, or brain cells. DMN (200 mg/kg) produced the highest frequency of 8AGr mutations in the embryo liver cells. After NME administration, there was marked increase in 8AGr mutations in brain cells. Detection of somatic mutations by HMTA is discussed. (45 Refs)

135. IN VIVO DAMAGE TO DNA: SEDIMENTATION STUDIES OF GIANT DNA MOLECULES FROM SOMATIC TISSUES.

Appleby DW, Appleby NH

Bethesda Res. Lab., Incorporated, P.O. Box 577, Gaithersburg, MD, 20760

Ecotoxicol Environ Saf; 5(4):443-451 1981

A method for detecting giant DNA molecules based on centrifugation at low speed for various periods of time to define the distribution of sedimentation coefficients in a cellular lysate is described. The lysate is constructed so as to preserve in vivo mol wt of DNA molecules. DNA molecules are separated in a centrifuge tube run in the preparative ultracentrifuge. The tube is then fractionated to de termine the positions occupied by the DNA. Data collected on Escherichia coli and Drosophila cells are reviewed. The major problem with application of the method to tissue biopsies is that DNA cannot be labeled in vivo to a sufficiently high specific activity. However, DNA can be detected after running the gradients by passing the individual fractions through nitrocellulose filters after denaturing the DNA. DNA bound to nitrocellulose and fixed can then be challenged with a short DNA sequence labeled to high specific activity in vitro. Short DNA sequences can then be identified. Use of this method with bacteriophage lambda DNA and the mouse satellite sequence is described. Application of the technique as a specific probe for the centromeres of chromosomes and for the whole chromosome may be possible. (11 Refs)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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CLINICAL STUDIES OF CHROMOSOMES IN HUMAN CANCER

1. ACUTE AND LONG-TERM CYTOGENETIC EFFECTS OF TREATMENT IN CHILDHOOD CANCER.

Aronson MM, Miller RC, Hill RB, Nichols WW, Meadows AT
(c/o Nichols), Inst. Medical Res., Camden, NJ, 08103
Mutat Res; 92(1/2):291-307 1982

The frequencies of chromosomal aberrations and sister chromatid exchanges (SCEs) in peripheral blood lymphocytes (PBL) were studied in 13 patients (1-18 yr old) receiving radiotherapy (RT) and/or chemotherapy for childhood cancer, in 17 long-term survivors (LTS) of childhood cancer whose last chemotherapy and/or RT had been given 6 mo-35 yr previously (3-7 yr in 10/17, 10-35 yr in 4/17), in 9 pediatric cancer patients who had not yet received RT or chemotherapy, and in 17 healthy subjects (2-73 yr old). In the combined control group, the mean SCE frequencies (4.0-9.6 SCEs/PBL) were the same in healthy subjects as in untreated cancer patients. Abnormal karyotypes were noted in 4/266 cells (0.015%) from the untreated cancer patients, in 42/332 cells (0.127%) from cancer patients receiving chemotherapy and/or RT, and in 9/433 cells (0.021%) from the LTS group. The abnormal karyotypes were usually chromosome breaks or structural rearrangements. Mean SCE frequencies were significantly above control values (3.3-33.7 SCEs/cell) in the cancer patients receiving treatment but not in the LTS group (means, 4.6-9.7 SCEs/cell). The numbers of SCE and breakage figures in the PBL of treated cancer patients varied widely from one patient to another, but treatment-induced increases in SCE figures were not necessarily correlated with increased levels of breakage-type chromosomal aberrations. The normal frequency of SCEs in the LTS group suggested that chromosomal damage leading to SCEs was either lost (through repair or selection) or could not be detected by the assay technique if the post-treatment interval was long. When these subjects were added to a larger group of LTS subjects, the frequency of chromosomal aberrations in the PBL (49/1,712 cells) was significantly above the control level. (62 Refs)

2. ACUTE LEUKEMIA AND CANCER OF THE BREAST.

Krulik M, Smadja N, Genet JY, Audebert AA, Canuel C, Debray J
(c/o Debray) Clinique Medicale A, Hopital Saint-Antoine, 184, rue du Faubourg Saint-Antoine, 75571 Paris Cedex, France
Sem Hop Paris; 58(9):513-520 1982

Two patients who developed acute leukemia following treatment for breast neoplasms are described. A 69-yr-old woman developed acute erythroleukemia 3 yr following treatment of breast cancer with mastectomy, local radiotherapy (50 grays), and melphalan (8 mg/day for 5 days, every 6 wk for 26 mo). Seventeen days after onset of treatment with prednisone, mercaptopurine, cytarabine, and rubidomycin, the patient died of infectious complications. Patient 2 was diagnosed as having acute lymphoblastic leukemia 4 mo following surgical treatment of a breast tumor. A preleukemic phase preceded the development of the actual leukemia. Cytogenetic anomalies were observed in patient 1: anomalies of one chromosome 2 and pericentric inversion of the other; presence of 3q-, 6q-, 7p+, 11p+; and loss of one each of 5, 4, 6, 7, 12, 17, and 21 chromosomes. No normal mitoses were observed; all cells were hypodiploid Only six mitoses were obtained from blood cultured from patient 2; four mitoses were 46XX normal and two were hyperdiploid. Cases of leukemia in patients previously treated for breast cancer with chemotherapy with or without radiotherapy (35 patients), radiotherapy alone (42), and surgery alone (14) are reviewed. It was suggested that the association of leukemia with breast cancer may be therapy-induced or spontaneous. (68 Refs) (In FRE)

3. ABNORMALITIES OF CHROMOSOME NO. 17 IN MYELOPROLIFERATIVE DISORDERS.

Borgstrom GH, Vuopio P, De la Chapelle A

Dept. Medical Genetics, Univ. Helsinki, Haartmaninkatu 3, 00290 Helsinki 29, Finland

Cancer Genet Cytogenet; 5(2):123-135 1982

In routine analyses, abnormalities of chromosome Number 17 were found in the bone marrow cells of 28 patients with Ph(1)-positive and 3 patients with Ph(1)-negative chronic myeloid leukemia (CML), 4 patients with acute nonlymphocytic leukemia (ANLL), and 4 patients with preleukemia. With three exceptions, all patients were in the blastic (CML) or the terminal phase. In 28 patients, the aberrant chromosome Number 17 arose by clonal evolution from the karyotype found at diagnosis or before the terminal phase. The abnormalities encountered were an isochromosome for the long arm, i(17q), (26 cases), translocations involving Number 17 (12 cases), trisomy 17 (3 cases), and ring 17 (1 case). In 35 patients, there was an unbalanced structural aberration of at least one of the Number 17 chromosomes. In every case (35/35), detailed analysis of the structurally abnormal Number 17 revealed loss of the distal part of the short arm (or possibly most of the short arm). Gain of the long arm (or at least its proximal part) was also common, but not invariably present (26/35). It is suggested that loss of 17p is a highly nonrandom event related to blastic crisis in CML and the terminal phase in other myeloid leukemias. (Author abstract) (26 Refs)

4. T(15;17) TRANSLOCATION IN ACUTE PROMYELOCYTIC LEUKEMIA (M3) AND CYTOLOGICAL 'M3-VARIANT'.

Berger R, Bernheim A, Daniel MT, Valensi F, Flandrin G

Laboratoire de Cytogenetique, Institut de Recherches sur les Leucemies, et les Maladies du Sang Hopital Saint-Louis, 2, place du Dr A-Fournier, F-75475 Paris Cedex 10, France

Nouv Rev Fr Hematol; 23(1):27-38 1981

Of 158 patients with nonlymphoblastic acute leukemia, 20 exhibited the t(15;17) chromosomal translocation. Of these 20 patients, 15 had M3-type acute promyelocytic leukemia (APL); 5 had the chromosomal translocation but did not fit normal cytological criteria for APL (M3-variant: M3var). Patients with M3 APL showed leukopenia or moderate hyperleukocytosis. Patients with M3var had marked hyperleukocytosis. Bone marrow aspirates from M3 patients were characterized by highly granular blast cells with irregular nuclei. 'Faggot cells' containing Auer bodies were found in varying numbers. Some patients had cells with small, single- or bi-lobed nuclei, suggesting different degrees of maturation among blast cells. Blast cell s from M3var patients, particularly cells from peripheral blood, were more faintly granular and generally large. Nuclei were irregular and cytoplasm was abundant. The general hematologic picture was similar to acute monocytic leukemia. One M3var patient had cytological characteristics intermediate between the other M3var patients and the M3 patients. M3 cells showed a positive chloroacetate esterase reaction; M3var cells were negative. Results suggest differences in maturation and kinetics of blast cells in M3 and M3var APL. (27 Refs)

5. CLONES WITH 3 PH1 AND 4 PH1 IN THE TERMINAL PHASE OF THREE CASES OF CHRONIC MYELOID LEUKEMIA.

Cabrol C, Peytremann R, Maurice PA
Univ. Inst. Medical Genetics, 8, chemin Thury, CH-1206 Geneva, Switzerland
Acta Haematol (Basel); 67(3):150-159 1982

G-banded cytogenetic studies of three male patients in the terminal phase of chronic myeloid leukemia showed the following abnormalities: in the first case, the presence of a medullar cell line with 51 chromosomes and 3 Ph1; in the second case, a clone with 65 chromosomes and 4 Ph1, and in the third patient a clone with 53 chromosomes and 3 Ph1. In all three cases, G-banding revealed the Ph1 translocation to be of the usual type: t(9;22) (q34;q11) and there was discordance between the number of Ph1 and 9q+. There was no obvious correlation between the presence of mutliple Ph1 and the clinical or cytological features. These three cases were detected as part of a recent G-banded cytogenetic survey of nine individuals in the blastic phase studied by the authors. The frequency of multiple Ph1 observed in this sample of blastic-phase leukemia is unusually elevated, raising the question of the origin of such a high incidence. (Author abstract) (12 Refs)

6. AN ANALYSIS OF CHROMOSOME FINDINGS IN NON-HODGKIN'S LYMPHOMAS.

Kaneko Y, Abe R, Sampi K, Sakurai M
(c/o Sakurai) Dept. Clinical Lab., Saitama Cancer Center, 818 Komuro, Ina, Saitama 362, Japan
Cancer Genet Cytogenet; 5(2):107-121 1982

Banding studies were done on tissues from tumors excised from 22 Japanese patients with non-Hodgkin's lymphomas. All tumors were found to be associated with aneuploidy. The chromosome abnormalities were diverse, with each chromosome type being involved in these abnormalities. Terminal deletions, derivative chromosomes as a result of unbalanced or non-reciprocal translocations, and markers of totally or partially unknown origin accounted for the majority of the structural abnormalities. Balanced reciprocal translocations were seen only occasionally. The 14q+, 6q-, partial trisomy of 1q, 11q+, 18q+, and 19q+ abnormalities were seen in more than two patients. The incidence of a missing sex chromosome was significantly higher than that of autosomes, but no particular other karyotypic abnormality seemed to be associate d with the event. All six patients whose chromosomes could be totally characterized were in complete remission. Patients with one or more markers of unknown origin (either totally or partially), had a median survival of only 8 mo (p less than 0.01). Five of the former six patients showed a nodular histology. Fifteen of the latter 16 patients had a diffuse histology, with 13 of the 15 having diffuse histiocytic lymphoma. The median survival of 9.5 mo for the 14 with only abnormal metaphases in the lymphatic tissues (AA-group) was shorter than the 26+ mo for the 7 patients with both normal and abnormal metaphases (AN-group). Thus certain aspects of chromosomal changes appear to correlate with histology and/or prognosis in non-Hodgkin's lymphomas. (Author abstract) (29 Refs)

7. CYTOGENETIC STUDIES ON FOUR CASES OF NON-ENDEMIC BURKITT LYMPHOMA.

Slater RM, Behrendt H, Van Heerde P
Inst. Human Genetics, Sarphatistraat 217, 1019 BX Amsterdam, The Netherlands
Med Pediatr Oncol; 10(1):71-84 1982

Cytogenetic studies carried out on four children with non-endemic Burkitt lymphoma showed: (1) two with the typical translocation t(8;14) (q24;1q32); (2) one with a variant t(2;8)(p11;24); and (3) one with apparently normal chromosomes 8 and 14. Additional chromosomal variation was present in all four patients. Two were shown to have a duplication of part of the long arm of chromosome 1 (1q23 to 1q32 and 1q23 to 1q42). Epstein Barr virus studies on two patients showed that one was positive and the other negative. A comparison of these results with other non-endemic cases in the literature has been made revealing a wider range of chromosomal variation than has been hitherto reported for endemic cases. The finding that chromosome 8 is also involved in the variant translocations in Burkitt lymphoma suggests that its changes may contribute more to the tumor development than the 14q+. (Author abstract) (40 Refs)

8. CYTOGENETIC STUDIES USING HPCM-STIMULATED SHORT-TERM LIQUID CULTURES OF CIRCULATING HEMOPOIETIC PRECURSOR CELLS IN PATIENTS WITH MYELOFIBROSIS.

Ganser A, Carbonell F

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Blut; 44(2):111-114 1982

Cytogenetic studies were performed on nine patients (5 men, 40-62 yr old and 4 women, 54-70 yr old) with myelofibrosis. Two men and one woman showed signs and symptoms of acute leukemia. Mononuclear cells were separated from samples of peripheral blood and cultured in medium conditioned with fresh human placenta (HPCM). Metaphase preparations were made after 2 days of incubation. Two patients showed evidence of chromosomal abnormalities. All metaphases in cell cultures from one patient with acute myeloid leukemia showed the loss of the Y chromosome. Cell cultures from a patient not showing si gns of leukemia showed an abnormal stem line with alterations of chromosomes 7 and 9 (46,XX,7q-,-9,+mar). Results indicate that culturing of hematopoietic cells in HPCM is suitable for determining whether myeloproliferative syndromes are the result of autochthonous proliferation and differentiation of stromal cells or of irreversible abnormalities of hematopoietic stem cells. Detection of abnormal clones indicates that myelofibrosis is a secondary effect of a neoplastic disorder. Absence of abnormal clones does not, however, rule out a leukemic process. (16 Refs)

9. CONTRIBUTIONS OF CYTOGENETICS IN THE STUDY OF HEMATIC NEOPLASIA.

Brieux de Salum S, Larripa I, Labal de Venuesa M, Slavutsky I, Bianchi de Di Risio C, Mudry de Pergament M

Departamento de Cultivo de Tejidos y Citogenetica, Instituto de, Investigaciones Hematologicas Academia Nacional de Medicina, Buenos Aires, Argentina

Medicina (B Aires); 41(Suppl):187-190 1981

Contributions of cytogenetics in the study of hematic cancer were noted including Boveri's, Nowell's, and Rowley's hypotheses, as well as Trosko's theory. Specific chromosomal anomalies in hematic cancer and their diagnostic and prognostic value, relationship between evolution of karyotype and increase in malignity, as well as between some chromosomal anomalies and etiology of malignity, and sister chromatid exchange were discussed. (46 Refs) (In SPA)

10. CYTOGENETIC STUDIES IN PRELEUKEMIC STATES.

Larripa I, Brieux de Salum S

Departamento de Tejidos y Citogenetica, Instituto de Investigaciones, Hematologicas Academia Nacional de Medicina, Buenos Aires, Argentina

Medicina (B Aires); 41(Suppl):179-186 1981

Chromosomal studies were evaluated for diagnosis and especially for prognosis of preleukemic states. Patients without previous treatment and without clinical or hematologic symptoms of leukemia included 20 patients with refractory anemia (RA), 7 with sideroblastic anemia (AS), 21 with polycythemia vera (PV). Ten patients with ferropenic anemia served as controls, because they have normal karyotypes. Of the 21 patients with PV, all had numerical cytogenetic alterations (CA) and in 17 they were associated with structural alterations (SA), but 15 were in good condition and 5 were stationary. Seven patients with AS had numerical CA; in two they were associated with SA; one of them with 7q developped acute myeloblastic leukemia (AML), the other was stationary, while five were in good condition. Of the 20 patients with the RA, 4 had polyploidy, 3 had diffuse chromosomes (DC), the rest had numerical CA associated in two of them with SA. The two patients with RA died without developping leukemia, one with DC and the other with CA associated with SA (r and 2q +). Four or the patients with RA developped AML, four were in poor condition, one was stationary, and nine were in good condition. Anomalous clones in cytopenic states indicate bad prognosis (high risk for leukemia or short survival), but they are not indicating for PV. (42 Refs) (In SPA)

11. BIBLIOGRAPHIC REVIEW AND OUR PERSONAL EXPERIENCE IN CYTOGENETIC STUDIES IN CHRONIC MYELOID LEUKEMIA.

Brieux de Salum S, Labal de Vinuesa M

Departamento de Cultivo de Tejidos y Citogenetica, Instituto de, Investigaciones Academia Nacional de Medicina, Buenos Aires, Argentina

Medicina (B Aires); 41(Suppl):170-178 1981

Chronic myeloid leukemia (CML) and the chromosomal anomaly Philadelphia chromosome 1 (Ph1) were discussed. Patients with CML had 77.5% Ph1 positive and 22.5% had Ph1 negative (-). The patients with Ph1-consisted usually of older men with low platelet, low WBC and shorter survival. Therapy for the patients with CML was also discussed. (46 Refs) (In SPA)

12. SEX CHROMATIN IN ONCOLOGICAL MORPHOLOGY.

Golovin DI, Zus BA

Dept. Pathology, Sanitary-Hygienic Inst., Leningrad, USSR

Arkh Patol; 43(12):3-8 1981

The role of sex chromatin (SC) in tumor development is reviewed. Comparative analysis of different histological variants of breast cancer showed that the rate of tumor proliferation is related to the number of nuclei containing SC bodies. The SC test could be used for determination of the proliferative activity in the tumors of the urothelium as well as for the differential diagnosis between follicular adenomas and highly differentiated follicular carcinomas of the thyroid. (39 Refs) (In RUS)

DNA CONTENT AND PLOIDY CHANGES ASSOCIATED WITH CANCER

13. FLOW CYTOMETRIC ANALYSIS OF DNA CONTENT OF BONE MARROW CELLS IN PATIENTS WITH PLASMA CELL MYELOMA: CLINICAL IMPLICATIONS.

Bunn PA, Krasnow S, Makuch RW, Schlam ML, Schechter GP
NCI-Navy Medical Oncology Branch, Natl. Naval Medical Center, Bestheda, MD, 20014
Blood; 59(3):528-535 1982

DNA content analysis by flow cytometry was performed in 32 patients with plasma cell myeloma and 3 patients with Waldenstrom's macroglobulinemia to determine the biologic and potential clinical usefulness of this technique. Hyperdiploid tumor DNA content was found in 23 myeloma patients (72%) during the course of illness, including 16/28 at presentation, but in none of 3 patients with Waldenstrom's macroglobulinemia. There was no significant association of aneuploidy in myeloma patients with age, sex, race, or M-protein class. Myeloma patients with aneuploid tumor cells were more likely to have advanced stage ($p = 0.032$) than patients with diploid plasma cells, and all patients with renal failure had aneuploid tumors. Pretreatment factors significantly associated with survival included stage ($p = 0.01$), serum creatinine ($p = 0.003$), and tumor DNA content ($p = 0.005$). Multivariate analysis using the Cox life table re gression procedure indicated that the significant relation of tumor DNA content with survival remained after adjusting for stage (p less than 0.005). Myeloma patients with diploid tumors at diagnosis frequently had aneuploid plasma cells at the time of relapse, indicating a possible relationship of chromosomal alterations in the tumor to clinical drug resistance. We conclude that aneuploid tumor cells at the time of diagnosis of myeloma are of independent prognostic significance, and the development of aneuploidy is a frequent occurrence at clinical relapse, suggesting the changes in DNA content are of biologic and clinical significance. (Author abstract) (29 Refs)

14. DNA PROFILE AND TUMOUR PROGRESSION IN PATIENTS WITH SUPERFICIAL BLADDER TUMOURS.

Gustafson H, Tribukait B, Esposti P
Dept. Urology, Karolinska Hosp., Stockholm, Sweden
Urol Res; 10(1):13-18 1982

Two hundred-twenty nine cases of surgically treated superficial bladder tumors Grade 1-2, category Ta or T1, were followed clinically and by flow cytofluorometry (FCM). The mean follow-up time for continuous FCM was 2.6 yr. Three different types of DNA pattern were found in Grade 2 tumors: diploid DNA pattern; tetraploid DNA pattern; and non-tetraploid types with hypo- and hypertetraploid patterns. One hundred-seventy five cases were diploid and 54 were aneuploid. Tumor progression was not seen in the 175 cases with repeatedly diploid DNA pattern. In the cases with tumor progression, the degree of ploidy could be related to the frequency of progression: 50% of the cases with triploid-hypotetraploid DNA pattern showed progression, while 10% with tetraploid DNA showed progression. FCM analysis in 33 cases of recurring tumors revealed that the degree of ploidy and the proportion of S-phase cells was fairly constant. The results indicate that the DNA profile can characterize a bladder tumor by its degree of ploidy and proliferation, and may be significant in predicting progression in cases of well and moderately well differentiated superficial bladder carcinoma. (11 Refs)

15. ACUTE LYMPHOCYTIC LEUKEMIA WITH MICROBLASTOSIS AND NEAR HAPLOIDY (26 CHROMOSOMES): A CASE REPORT.

Hoeltge GA, Dyment PG, Slovak ML
Dept. Lab. Hematology, Cleveland Clinic Foundation, 9500 Euclid St., Cleveland, OH, 44106
Med Pediatr Oncol; 10(1):53-59 1982

A 3-year-old acute lymphocytic leukemia (ALL) patient had a modal chromosome count of 26 in her bone marrow metaphases. The leukemia was 'common' ALL by cytochemical and immunologic studies. Five other cases had been reported previously, and all have had a near haploidy varying from 26 to 32 chromosomes. Disomy of chromosomes 18 and 21 is a consistent feature of this disease. Severe hypodiploidy correlates with microblastosis requiring morphologic separation from non-neoplastic small lymphocytes. (Author abstract) (16 Refs)

CHROMOSOMAL FRAGILITY AND GENETIC FACTORS PREDISPOSING TO HUMAN CANCER

16. NUMERICAL AND STRUCTURAL CHROMOSOME ABERRATIONS IN CULTURED LYMPHOCYTES AND CUTANEOUS FIBROBLASTS OF PATIENTS WITH MULTIPLE ADENOMAS OF THE COLORECTUM.

Gardner EJ, Rogers SW, Woodward S
Dept. Biology, Utah State Univ., Logan, UT, 84322
Cancer; 49(7):1413-1419 1982

Excessive random loss and gain of single chromosomes at the diploid and tetraploid levels, and numerous chromosomal aberrations, have been observed in lymphocytes and fibroblasts, cultured from Gardner syndrome and familial polyposis coli patients and children at risk for multiple adenomas. This increase in numerical and structural aberrations seems to represent a general instability of chromosomes in the lymphocyte and fibroblast nuclei of patients with multiple adenomas in the colorectum. A consistent heteromorphism of chromosome No. 2 homologues tentatively identified as a deletion was observed in all 17 patients with multiple adenomas in the colorectum, and two younger people of 13 and 6 yr of age who are at risk for Gardner syndrome but do not have colorectal polyps. The chromosome No. 2 aberration was not observed in two symptomatic patients with occasional discrete colorectal adenomas. Eighteen controls who did not have Gardner syndrome nor familial polyposis coli did not show the structural aberration in chromosome No. 2 nor chromosome instability. (Author abstract) (21 Refs)

17. INTERCALARY DELETION OF THE SHORT ARM OF CHROMOSOME 11: ANIRIDIA, GLAUCOMA, GROWTH AND MENTAL RETARDATION, SEXUAL AMBIGUITY, GONADOBLASTOMA, AND CATALASE DEFICIENCY.

Dufier JL, Le-hoang-Phug, Schmelck P, Fekete C, Turleau DG, Haye C, Guillaumat
No affiliation given
Bull Soc Ophtalmol Fr; 81(10):747-749 1981

Deletion of chromosome 11 p13 and catalase deficiency were found in a 20-mo-old male who presented with aniridia, glaucoma, mental and growth retardation, sexual ambiguity, and gonadoblastoma, but no evidence of Wilms' tumor. Ophthalmological and general findings are reported. The significance of the chromosome deletion is discussed in relation to the resulting syndrome. (6 Refs) (In FRE)

18. EFFECTS OF AGE, SEX AND GENES ON SISTER CHROMATID EXCHANGE.

Waksvik H, Magnus P, Berg K

Dept. Genetics, Norsk Hydro's Inst. Cancer Res., Montebello, Oslo 3, Norway

Clin Genet; 20(6):449-454 1981

Sister chromatid exchange (SCE) was studied in cultured lymphocytes from a limited series of 21 like-sexed twin pairs; 11 monozygotic (MZ) and 10 dizygotic (DZ) pairs. The 18 subjects, who were between 57 and 61 yr old, had an SCE mean value of 8.0 whereas the 24 subjects between 33 and 39 yr of age had a mean of 6.8. The difference was statistically significant (p less than 0.001). The effect of age appeared to be present in both sexes. No significant difference was found between females (mean = 7.3) and males (mean = 7.5), nor between smokers (mean = 7.3) and non-smokers (mean = 7.4). Drug users had a slightly higher mean (7.9) than non-users (7.0) (p less than 0.05). This trend was found in each age group. The within-pair variance was slightly higher in DZ than in MZ pairs. The difference was not significant. We conclude that genetic factors are probably not a major source of subject variation in SCE mean value. (Author abstract) (18 Refs)

19. A FAMILY STUDY OF SPONTANEOUS SISTER CHROMATID EXCHANGE FREQUENCY.

Cohen MM, Martin AO, Ober C, Simpson SJ

Div. Genetics, Dept. Pediatrics, Children's Memorial Hosp., 2300 Children's Plaza, Chicago, IL, 60614

Am J Hum Genet; 34(2):294-306 1982

The frequencies of spontaneous sister chromatid exchanges (SCEs) were studied in phytohemagglutinin-stimulated peripheral lymphocytes of 52 subjects (Ss) belonging to 12 nonconsanguineous 2-generation families. Three generations of two families were studied. The Ss had no major health problems requiring treatment, no neoplasms, and no known genetic disorders. Their occupations involved no known exposure to SCE-inducing agents. All but two of the Ss were non-smokers. Repeated tests in several Ss disclosed no significant variations in SCE frequency over the 8-mo study period. The mean familial SCE frequencies varied widely (0.118-0.201 SCEs/chromosome), but mean SCE frequencies within a given sibship did not. Comparisons of the SCE frequencies in parents and children disclosed significant correlations in mother-son and father-daughter pairs, but not in father-son pairs, suggesting X-linkage of the trait. No correlation was observed between the SCE frequencies of husbands and wives, although they shared the same environments. Further studies involving a larger sample of multiple-generation families should be helpful in investigating the possibility of a genetic control of the SCE frequency. (38 Refs)

20. ABNORMAL LEVELS OF UV-INDUCED UNSCHEDULED DNA SYNTHESIS IN ATAXIA TELANGIECTASIA CELLS AFTER EXPOSURE TO IONIZING RADIATION.

Jaspers NG, Bootsma D
Lab. Cell Biology and Genetics, Erasmus Univ. Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands
Mutat Res; 92(1/2):439-446 1982

The baseline levels of UV-induced unscheduled DNA synthesis (UDS) in normal human fibroblast cell lines (C3RO and C5R0) and ataxia-telangiectasia (AT) fibroblast cell lines (AT5BI, AT4BI, AT2BE, AT1PWA, and AT3BI) were determined to be same. Exposure to x-rays (XR: up to 20,000 rads) significantly altered UV-induced UDs in the AT cells but not in the normal cells. In AT cell lines showing a reduced capacity for gamma-ray-induced repair DNA synthesis (excision-deficient AT cell lines AT3BI and AT2BE), XR exposure inhibited UV-induced UDS. In AT cell lines showing a normal capacity for gamma-ray-induced repair DNA synthesis (excision-proficient AT cell lines), XR exposure stimulated UV-induced UDS. The excision-deficient and excision-proficient AT cell lines showed different dose-response relationships for both UV and XR. The two types of AT cells may have different molecular defects. Altered levels of repair DNA synthesis after UV exposure in AT cells may be secondary consequences of the way the cells handle DNA damage induced by ionizing radiation. (14 Refs)

21. THE EFFECT OF BLEOMYCIN ON DNA SYNTHESIS IN ATAXIA TELANGIECTASIA LYMPHOID CELLS.

Cohen MM, Simpson SJ
Div. Genetics, Children's Memorial Hosp., 2300 Children's Plaza, Chicago, IL, 60614
Environ Mutagen; 4(1):27-36 1982

The effect of bleomycin (BLM) on DNA synthesis was determined in (methyl-3H)thymidine-labeled lymphoid cells from five patients with ataxia telangiectasia (AT) and three patients with xeroderma pigmentosum (XP) compared to those from four normal subjects. BLM (5, 10, 25 and 50 ug/ml) treatment of AT cells over a period of 4 hr led to some inhibition of incorporation compared to normal cells. DNA synthesis of AT cells determined at hourly intervals after exposure to BLM (1, 5, 10, and 25 ug/ml) showed that AT cells did not attain normal levels during the 24-hr observation period whereas normal cells recovered within 15-18 hr. These differences were not found after exposure of the cells to mitomycin C. Following BLM treatment and preincubation with hydroxyurea, residual DNA synthesis was similar in AT, XP and normal lymphoid cells, suggesting that the capacity to repair the induced DNA lesion is present. (30 Refs)

22. TRANSFECTION OF CELLS FROM A XERODERMA PIGMENTOSUM PATIENT WITH NORMAL HUMAN DNA CONFERS UV RESISTANCE.

Takano T, Noda M, Tamura TA
Dept. Microbiology, Keio Univ. Sch. Medicine, Shinjuku-Ku, Tokyo-160, Japan
Nature; 296(5854):269-270 1982

Transfection of cells from a patient with xeroderma pigmentosum (XP) by DNA from normal human cells produced cells which were resistant to UV damage. XP20S skin fibroblasts from a XP patient were transformed by simian virus 40 (SV40) and established as a permanent cell line, XP20S(SV). The activity transforming the XP cells to UV resistance (UVr) was carried on the DNA molecules introduced into the transformed cells, because after treatment of donor A204 DNA with DNase I, there were very few UVr transformants. The sensitivity of the transforming activity of A204 DNA was tested with various restriction enzymes which recognize different hexanucleotide sequences at their cleavage sites. SalI and XhoI raised transformation efficiency whereas HindIII, BamHI and EcoRI removed the transforming activity. Many minute colonies were found in cultures treated with BamHI- and HindIII-digested DNAs; these digested DNAs appeared to slightly raise the UV-resistance of the recipient cell. UV-resistant XP20S(SV) cells transformed by both high-mol wt and restriction endonuclease-cleaved DNA from DNA donors A204 and MRC-5 showed stable UVr phenotypes during passage in culture; no revertants that were highly sensitive to UV were found. The resistant cells have presumably acquired a gene conferring UV resistance. (6 Refs)

23. INACTIVATION OF ULTRAVIOLET REPAIR IN NORMAL AND XERODERMA PIGMENTOSUM CELLS BY METHYL METHANESULFONATE.

Cleaver JE
Lab. Radiobiology and Environmental Health, Univ. California, San Francisco, San Francisco, CA, 94143
Cancer Res; 42(3):860-863 1982

Excision repair of ultraviolet damage in the DNA of normal and xeroderma pigmentosum (Groups C, D and variant) cells was inactivated by exposure of cells to methyl methanesulfonate immediately before irradiation independent of the presence of 0 to 10% fetal calf serum. The inactivation could be represented by a semilog relationship between the amount of repair and methyl methanesulfonate concentration up to approx 5 mM. The inactivation can be considered to occur as the result of alkylation of a large (about 10(6) daltons) repair enzyme complex, and the dose required to reduce repair to 37% for most cell types was between 4 and 7 mM. No consistent, large difference in sensitivity to methyl methanesulfonate was found in any xeroderma pigmentosum complementation group compared to normal cells, implying that reduced repair in these groups may be caused by small inherited changes in the amino acid composition (ie, point mutations or small deletions) rather than by losses of major components of the repair enzyme complex. (Author abstract) (19 Refs)

24. INDUCTION AND REPAIR OF PSORALEN CROSS-LINKS IN DNA OF NORMAL HUMAN AND XERODERMA PIGMENTOSUM FIBROBLASTS.

Bredberg A, Lambert B, Soderhall S
Dept. Clinical Genetics, Karolinska Hosp., S-104 01 Stockholm, Sweden
Mutat Res; 93(1):221-234 1982

Induction and repair of DNA damage produced by exposure to 8-methoxypsoralen (8-MOP) was studied in normal human fibroblasts and fibroblasts of the xeroderma pigmentosum (XP) line CRL 1223. Cells were labeled with [methyl-3H]thymidine. DNA damaged was assessed by alkaline elution. Cells were treated with UV-A irradiation, PUVA (8-MOP + UV-A), PUVA + UVA (PUVA + UV-A alone 1 or 7 days after PUVA), or x-rays. Cells were exposed to 8-MOP (1 or 20 ug/ml) at 37 C for 1 hr. UV-A irradiation (0.04 or 1.1 Joules/square cm) was carried out at 0-4 C. UV-A treatment increased the elution rate of DNA; the increase returned to normal in cells incubated for 30 min after irradiation. Elution rates for cells treated with PUVA were not different from those for controls. Elution rates for cells treated with PUVA + UVA were initially below c ontrol values; during post-treatment incubation elution rates increased above control levels for 7 days. Elution rates for XP cells did not change during post-treatment incubation. Results indicate that UV-A irradiation produces DNA breaks that are rapidly repaired during post-treatment incubation. PUVA treatment produces monoadducts of DNA that last for up to 7 days; subsequent UV-A treatment converts the monoadducts to DNA cross-links. Cross-links are repaired by a process involving formation of DNA breaks. XP cells do not repair DNA damage. (23 Refs)

25. XERODERMA PIGMENTOSUM VARIANTS.

Cleaver JE, Coriell LL, Mulivor RA
(c/o Greene), Inst. Medical Res., Copewood St., Camden, NJ, 08103
Cytogenet Cell Genet; 31(3):188-192 1981

Xeroderma pigmentosum (XP) consists of the subgroups A, B, C, D, E, F, G, and variant. The first seven subgroups have a defect in the mechanisms of excision repair of DNA damage by UV radiation. The XP variant subgroup has normal excision repair but abnormal replication of UV-damaged DNA. The defect may be the loss of a gene product required for replication past damaged sites. Cultures of XP variant cells from a variety of ethnic groups and geographical areas are available and should be useful for investigating actinic carcinogenesis in XP. (26 Refs)

26. FAILURE OF RNA SYNTHESIS TO RECOVER AFTER ULTRAVIOLET IRRADIATION: AN EARLY DEFECT IN CELLS FROM INDIVIDUALS WITH COCKAYNE'S SYNDROME AND XERODERMA PIGMENTOSUM.

Mayne LV, Lehmann AR
(c/o Lehmann) MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton, Sussex BN1 9QG, England
Cancer Res; 42(4):1473-1478 1982

Previous work has shown that in cells from the UV-sensitive genetic disorder, Cockayne's syndrome, DNA synthesis fails to recover after UV irradiation, despite the fact that these cells have no detectable defect in either excision or daughter-strand repair pathways. We now show that Cockayne cells, as well as cells from a number of patients with xeroderma pigmentosum, are sensitive to the lethal effects of UV irradiation in stationary phase under conditions in which no DNA is synthesized after irradiation. Furthermore, in normal and defective human fibroblasts, RNA synthesis is depressed after UV irradiation. In normal (dividing) cells, RNA synthesis recovers very rapidly, but this recovery does not occur in Cockayne cells, and it is reduced or absent in xeroderma pigmentosum cells from different complementation groups. Qualitatively, similar results are obtained with cells in stationary phase. The recovery of RNA synthesis in the various defective cell strains is not correlated with the overall extent of excision repair, but there is some correlation between recovery of RNA synthesis and cell survival after UV irradiation. These results implicate recovery of RNA synthesis as an important early response to UV irradiation. (Author abstract) (3 3 Refs)

27. A DEFICIENCY IN THE REPAIR OF UV AND GAMMA-RAY DAMAGED DNA IN FIBROBLASTS FROM COCKAYNE'S SYNDROME.

Rainbow AJ, Howes M
Dept. Radiology, McMaster Univ., Hamilton, Ontario L8S 4J9, Canada
Mutat Res; 93(1):235-247 1982

DNA-repair deficiencies were investigated in fibroblasts from five unrelated patients with Cockayne's syndrome (CS) and two patients heterozygous for CS. Suspensions of adenovirus type 2 were exposed to UV or gamma irradiation. Fibroblasts were then infected with irradiated or nonirradiated virus and then incubated. The fibroblasts were then assayed by immunofluorescence methods for expression of viral structural antigens. Results obtained from CS fibroblasts were compared with results obtained from normal and xeroderma pigmentosum (XP) fibroblasts. Host-cell reactivation (HCR) of viral function for both UV- and gamma-irradiated virus was reduced in homozygous CS fibroblasts. The dose of UV required to reduce viral function in homozygous CS fibroblasts by 37% (D37) was 14-35% of the D37 for normal cells. D37 for gamma-irradiation of CS cells was 61-80% of that for normal cells. One heterozygous CS strain had a D37 for UV-irradiated virus 68% of normal, intermediate between the D37 for homozygous CS and normal cells. The other heterozygous CS strain had a normal D37. Results indicate that CS fibroblasts have a defect in DNA repair mechanisms. (41 Refs)

28. GIANT MARKER CHROMOSOME IN FANCONI'S ANEMIA TRANSFORMING INTO ERYTHROLEUKEMIA IN AN ADULT.

Rotzak R, Kaplinsky N, Chaki R, Blei F, Berkowitz M, Goldman B, Frankl O
Dept. Medicine, Chaim Sheba Medical Center, Tel-Hashomer, Israel
Acta Haematol (Basel); 67(3):214-216 1982

A 22-yr-old patient diagnosed as having Fanconi's plastic anemia turning to acute erythroleukemia is described. The diagnosis was based on congenital malformations, pancytopenia and the known chromosomal abnormalities. We call attention to the patient's age at time of diagnosis, the turn into erythroleukemia, the cataracts and the giant marker chromosome in bone marrow cells - features that make this patient exceptional. (Author abstract) (10 Refs)

29. REPAIR AND REPLICATION OF DNA IN HEREDITARY (BILATERAL) RETINOBLASTOMA CELLS AFTER X-IRRADIATION.

Cleaver JE, Char D, Charles WC, Rand N
Lab. Radiobiology and Environmental Health, Univ. California, San Francisco, CA, 94143
Cancer Res; 42(4):1343-1347 1982

Fibroblasts from patients with hereditary retinoblastoma reportedly exhibit increased sensitivity to killing by x-rays. Although some human syndromes with similar or greater hypersensitivity to DNA-damaging agents (eg, x-rays, ultraviolet light, and chemical carcinogens), such as xeroderma pigmentosum, are deficient in DNA repair; most do not have such clearly demonstrable defects in repair. Retinoblas toma cells appear to be normal in repairing single-strand breaks and performing repair replication after x-irradiation and also in synthesizing poly(adenosine diphosphoribose). Semiconservative DNA replication in these cells, however, is slightly more resistant than normal after x-irradiation, suggesting that continued replication of damaged parental DNA could contribute to the pathogenesis of the disease. This effect is small, however, and may be a consequence rather than a cause of the fundamental enzymatic abnormality in retinoblastoma that causes the tumorigenesis. (Author abstract) (42 Refs)

30. RETINOBLASTOMA: CLINICAL AND HISTOPATHOLOGIC FEATURES.

Sang DN, Albert DM
Massachusetts Eye and Ear Infirmary, Harvard Medical Sch., 243 Charles St., Boston, MA, 02114
Hum Pathol; 13(2):133-147 1982

Retinoblastoma, the ocular tumor of childhood, is unusual in its genetic implications, the frequency of occurrence of second primary tumors, the association of a 13q14 chromosome deletion, and the high incidence of spontaneous regression. This article reviews the clinical and histopathologic features of the disease and briefly summarizes histopathologic findings regarding cell death and tumor necrosis in retinoblastoma. (Author abstract) (163 Refs)

CHROMOSOMES OF HUMAN CELL LINES AND TUMORS IN VITRO

31. CHARACTERIZATION OF A NEWLY ESTABLISHED HUMAN GASTRIC CANCER CELL LINE HGT-1 BEARING HISTAMINE H2-RECEPTORS.

Laboisse CL, Augeron C, Couturier-Turpin MH, Gespach C, Cheret AM, Potet F
Laboratoire de Biologie et de Physiologie des Cellules Digestives, U 239 INSERM, Faculte de Medecine Xavier Bichat, 16 rue Henri Huchard, 75018 Paris, France
Cancer Res; 42(4):1541-1548 1982

A human gastric adenocarcinoma cell line, HGT-1, was established in vitro from the primary tumor of a 60-yr-old patient. Histological examination of the tumor revealed a poorly differentiated adenocarcinoma. Primary tumor cells were cloned in soft agarose and gave rise to tumor colonies. The procedures enabling us to form a continuous cell line from the agarose colonies are described. The cultured cells grew as monolayers of closely apposed polygonal cells with a population-doubling time of 19.48 +-1.20 (SE) hr during exponential growth at passage 59. They had an epithelial morphology. Ultrastructural studies revealed the presence of microvilli and tight junctions. The HGT-1 cell line is tumorigenic in nude mice and has a hyperdiploid karyotype with a modal number of 57 chromosomes. It exhibits numerous marker chromosomes. These human gastric epithelial cells do not secrete mucus or carcinoembryonic antigen. They exhibit functional histamine H2-receptors mediating cellular cyclic adenosine 3':5'-monophosphate production and adenylate cyclase activation. In conclusion, the use of a soft-agarose clonogenic assay permitted us to develop a cancer cell line without the problems of fibroblastic cell contamination. The existence of histamine H2-receptors on gastric HGT-1 cells stresses the importance of this line as a model for studies of regulatory mechanisms involved in gastric secretion. (Author abstract) (39 Refs)

32. ESTABLISHMENT AND CHARACTERIZATION OF AN EPSTEIN-BARR VIRUS-NEGATIVE LYMPHOMA B-CELL LINE FROM A PATIENT WITH A DIFFUSE LARGE CELL LYMPHOMA.

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Cancer Res; 42(4):1368-1373 1982

Cell line (LNPL) was established from a tumor biopsy of a nasopharyngeal 'histiocytic' lymphoma composed of large noncleaved B-cells. LNPL expressed immunoglobulin M kappa surface immunoglobulin, as did the original tumor. LNPL also expressed Ia antigen but lacked Epstein-Barr virus nuclear antigen. It exhibited a translocation between chromosomes 8 and 14 which has been described in certain other malignant lymphoproliferative disorders. An autologous T-cell line lacked the translocation between chromosomes 8 and 14. LNPL is being used as an immunogen to produce monoclonal antibodies in our laboratory. Such cell lines may facilitate identification of lymphoma-associated surface antigens. (Author abstract) (36 Refs)

33. ESTABLISHMENT OF A HUMAN CELL LINE (B-25F) DERIVED FROM A FIBROMA OF BUCCAL EPITHELIUM.

Blasko M, Kuliffay P, Bizik J, Zajac V, Grofova M, Matoska J, Thurzo V
Cancer Res. Inst., Slovak Acad. Sciences, 812 32 Bratislava, Czechoslovakia
Neoplasma; 28(6):675-684 1981

A new cell line (B-25F) obtained from a benign polypoid fibrous lesion of the mucosa of oral cavity is described. The cells at first grew in suspension but after a mo of cultivation they began to adhere and subsequently formed a monolayer typical for fibroblastoid cells. Population doubling time both in lower and higher passages was 60 hr. Electron microscopy studies failed to detect any viral particles or mycoplasmas. A comparison of cell surface glycoproteins of fibroblasts (B-41FB), fibroma cells (B-25F), and fibrosarcoma cells (B-6FS) was made. These lines share common traits in their surface membranes although distinct differences among the individual lines could be detected. Karyological analysis showed that 64% of cells contained 46 chromosomes. This number veiled both diploid and pseudodiploid karyotypes. An aberrant chromosome, t(13;18?) was found. For isoenzyme comparison of B-41FB, B-25F, B-6FS, and HeLa cell lines the mobility of lactate dehydrogenase (LDH) and glucose-6-phosphate dehydrogenase (G-6-PD) was employed. All these lines had LDH patterns of human cells, and a G-6-PD pattern of phenotype B except that of HeLa cells that had phenotype A. (Author abstract) (17 Refs)

34. ANCHORAGE INDEPENDENT GROWTH OF SV40 TRANSFORMED HUMAN EPITHELIAL CELLS FROM AMNIOTIC FLUIDS: DIFFERENCES WITHIN AND AMONG CELL DONORS.

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In Vitro; 18(3):203-212 1982

Cells from seven individuals were cultured separately from the induction of morphological transformation by SV40. Sixty-three transformed colonies were tested for anchorage independent growth in soft agar at various passage levels. Colony formation was consistent for all clones of respective cell donors. Four donors yielded clones that grew in soft agar in the first passage. Clones from three donors were similar to controls and formed no colonies. The size of the agar colonies was constant in the early passages. Size differences were observed in later passages and for negative clones that gained anchorage independence during time in culture. The early passage positive type of anchorage independence is expressed concomitantly with morphological transformation. Considering that the clonal isolates are genetically homogeneous within cell donors and heterogeneous among cell donors, it is concluded that the phenotype of anchorage independence is determined by at least two genetic mechanisms; namely, the genotype of the cell donor (the hereditary type) or by culturally derived new genetic variability, or both. Family history on cancer incidence showed that one grandparent for each of the four positive donors for the hereditary type of anchorage independence had cancer, whereas the grandparents of the three negative donors were asymptomatic. The incidence of cancer did not appear to be age related. Chromosome analyses of two morphologically transformed colonies from each of the cell donors by the in situ technique, showed diploid and tetraploid cells and a small number of cells with rearrangements. It is concluded as previously that the progenitor transformed cell to the colony of cells is normal diploid. (Author abstract) (37 Refs)

35. OBSERVATIONS ON NUCLEAR PROTRUSIONS AND THE LENGTH OF LONG ARMS OF ABNORMAL CHROMOSOMES IN MALIGNANCY.

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Acta Cytol (Baltimore); 26(2):247-250 1982

The relationship between the appearance of nuclear protrusions and the length of the long arms of large abnormal chromosomes in preparations from cancer cells is described. Nuclear protrusions were found consistently in all cases in which there were cells with marker chromosomes having long arms at least as long as 85% of the whole of chromosome number 1. (Author abstract) (14 Refs)

CHROMOSOMES OF ANIMAL CELL LINES AND TUMORS

36. NUCLEOLUS ORGANIZER REGIONS IN DIPLOID AND HETEROPLOID CHINESE HAMSTER CELL LINES.

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Cytologia (Tokyo); 46(4):809-816 1981

By means of quinacrine mustard banding in conjunction with silver staining, active nucleolus-organizer regions (NOR) were identified on chromosomes 3, 4, 5, 7, 8, and 9 in the diploid CHFP-WG Chinese hamster cell line. The AK412 Chinese hamster cell line, which displays gross chromosomal rearrangements, carried NOR on only four of these chromosomes (one chromosome 4, two chromosomes 5, and both arms of iso 8p). Findings suggest suppression of some ribosomal RNA genes. (19 Refs)

37. INDUCTION OF CYTOTOXICITY, MUTATION, CYTOGENETIC CHANGES, AND NEOPLASTIC TRANSFORMATION BY BENZO(A)PYRENE AND DERIVATIVES IN C3H/10T1/2 CLONE 8 MOUSE FIBROBLASTS.

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Cancer Res; 42(5):1866-1875 1982

Benzo(a)pyrene (BaP), a series of its metabolic derivatives, and benzo(e)pyrene, a very weakly carcinogenic isomer, were tested for their biological effects on transformable C3H/10T1/2 cells. These cells were used as targets in a series of assays designed to measure oncogenic transformation, mutation to ouabain resistance, cytotoxicity, and induction of cytogenetic changes, as evidenced by chromosomal aberrations and sister chromatid exchange. Of all the compounds tested, only the parent hydrocarbon, BaP, and (+-)-trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene were found to be significantly active in producing transformation and cytogenetic alterations. BaP, (+-)-trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene, and (+-)-7alpha,8beta-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a)pyrene however, were all effective inducers of mutation in C3H/10T1/2 cells. (+-)-7alpha,8beta-Dihydroxy-9beta,10beta-epoxy-7,8,9, 10-tetrahydrobenzo(a)pyrene was the most potent agent in tests for cytotoxicity Benzo(e)pyrene was inactive in all assays examined. Among the compounds tested, there was a correlation between the ability to induce cytogenetic changes and the ability to produce mutation and transformation. These results support the demonstrated role of (+-)-trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene as a proximal carcinogenic form of BaP and illustrate the utility of the C3H/10T1/2 cell system as an important tool for the detection of genotoxic damage by carcinogenic chemicals. (Author abstract) (47 Refs)

38. CHARACTERIZATION OF HIGH- AND LOW-METASTATIC CLONES DERIVED FROM A METHYLCHOLANTHRENE-INDUCED MURINE FIBROSARCOMA.

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Cancer Res; 42(3):1046-1051 1982

A methylcholanthrene-induced fibrosarcoma (3AM) and several of its clones were evaluated for pulmonary metastasis, growth rate, and chromosome composition. Heterogeneity was observed in the three parameters, and no correlation was found between growth rate and metastatic potential. Furthermore, three clones (10, 34, and 27) were identified with distinctive, high or low, metastatic potential and marker chromosomes. The marker chromosomes characteristic for each clone were identified in the early passages of the parental 3AM line, indicating the preexistence of the different cell types in the original neoplasm. The three clones were then characterized as to tendency to adhere to vascular endothelium, immunogenicity, and antigenic specificity. Clone 10, with two large metacentric markers (T2, 4 and T10, 15) and the highest metastatic potential (221 foci/lung), expressed the highest endothelial attachment and immunogenicity. Clone 27 was characterized with an extremely low rate of metastasis (9 foci/lung) and a T2,7 large acrocentric marker, while clone 34 was characterized with a moderate rate of metastasis (107.5 foci/lung) and a T4,16 acrocentric marker. Antigenically, clone 10 cross-reacted with clones 34 and 27 and 3AM, while clones 27 and 34 crossreacted with clone 10 and 3AM but not with each other, suggesting that, within the original tumor, there were common tumor antigens shared by some cells but no universal antigen shared by all cells. (Author abstract) (20 Refs)

39. ELEVATED SISTER CHROMATID EXCHANGE RATE IN LYMPHOCYTES OF THE EUROPEAN EEL (ANGUILLA ANGUILLA) WITH CAULIFLOWER TUMOR.

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Cancer Genet Cytogenet; 5(2):137-145 1982

Sister chromatid exchange (SCE) frequency and chromosomal aberration was studied in cultured lymphocytes from the European eel (Anguilla anguilla) with cauliflower tumors. SCE was significantly increased in the affected fishes compared with normal controls, whereas chromosomal aberration did not. In comparison to normal cells, the lymphocytes responding to phytohemagglutinin M (PHA-M) in cultures from tumorous eels showed no evidence of cell cycle retardation. A possible mechanism for elevation of SCE and the significance of this finding relation to the etiology were discussed. (Author abstract) (38 Refs)

40. BIOLOGICAL CHARACTERISTICS AND VIRAL SUSCEPTIBILITY OF A STABLE DOG KIDNEY CELL LINE.

Fieldsteel AH, Nelson-Rees WA, Colston MJ
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In Vitro; 18(3):220-226 1982

A cell line derived in 1956 from normal dog kidney is described. The cells are epithelial, contact-inhibited, and can be maintained in the same culture vessels for periods of more than 2.5 y r. Karyologically, the cells are hypodiploid with a modal number of 72 as opposed to the diploid number of 78. The karyotype indicates male origin of the cells and clonal derivation of extant cultures due to the presence of two marker chromosomes in all metaphases observed. At the 159th passage the dog kidney (DK) cells did not produce tumors in athymic rats. At least 13 viruses of various types produced transmissible cytopathogenic effects in the DK cells, including all of the human influenza viruses investigated. (Author abstract) (23 Refs)

41. RADIOSENSITIVITY AND LIFE SPAN OF DOG PERIPHERAL BLOOD LYMPHOCYTES.

Leonard A, Decat G, Fritz TE
Mammalian Genetics Lab., Dept. Radiobiology, C.E.N.-S.C.K., B-2400 Mol, Belgium
Mutat Res; 92(1/2):257-263 1982

Phytohemagglutinin-stimulated peripheral blood lymphocytes (PBL) from two dogs were observed to enter the cell cycle shortly after initiation of the cultures. After 48 hr of cultivation, 52% were in the second mitosis and 17% in the third mitosis. In PBL cultures exposed to x-rays (200 rads), the mean corrected frequency of dicentric chromosomes after 48 hr (28.6%) was about the same as the yield of dicentrics observed in cultured human lymphocytes in the first mitosis (32%). Total-body irradiation (150 rads, 60Co) caused a sharp decline in peripheral lymphocyte counts. Lymphopenia persisted for up to 35 days, but the counts returned to normal by day 50. On day 14 after irradiation, dicentric figures were observed in 16-21% of the PBL. The estimated half-life of PBL carrying chromosome aberrations is less than 30 days. (17 Refs)

42. FORMATION OF CHROMOSOME-TYPE ABERRATIONS AT THE FIRST CLEAVAGE AFTER MMS TREATMENT IN LATE SPERMATIDS OF MICE.

Tanaka N, Katoh M, Iwahara S
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Cytogenet Cell Genet; 31(3):145-152 1981

Male mice were treated with graded dose of methyl methanesulfonate (MMS) and mated with untreated female mice during the 6 to 10 days after treatment. The nature of the primary lesions induced in late spermatids was investigated by analyzing the types and rates of chromosome aberrations in the first cleavage metaphases. The chromosome aberrations recovered at the first cleavage were predominantly of the chromosome-type. Their frequency increased exponentially with increasing dose of MMS. The results suggest that the nonenzymatic conversion of DNA containing alkylated bases to new damage, possibly strand breaks, during the maturation and storage of sperm was primarily responsible for the enhancement of the frequency of chromosome-type aberrations. (Author abstract) (28 Refs)

GENE MAPPING STUDIES

43. ASSIGNMENT OF AN OLIGOMYCIN-RESISTANCE LOCUS TO HUMAN CHROMOSOME 10.

Webster KA, Oliver NA, Wallace DC
Dept. Genetics, Stanford Univ., Sch. Medicine, Stanford, CA, 94305
Somatic Cell Genet; 8(2):223-244 1982

An oligomycin-resistant variant (HTO1AP) of human fibrosarcoma HT1080 was isolated and characterized. The mutant was nuclear, codominant, stable, and not cross-resistant to respiratory inhibitors. The mutant contained a mitochondrial ATPase which was less sensitive to oligomycin than that of wild type cells. Hybrids were produced between the human mutant and an 8-azaguanine-resistant derivative of a mouse BALBcd renal adenocarcinoma. The hybrids were oligomycin resistant (ARO), hypoxanthine-aminopterin-thymidine resistant, or resistant to both. A detailed karyotypic analysis of the ARO hybrids using trypsin-Giemsa staining revealed that resistance to oligomycin correlated with the retention of two human chromosomes 10. Analyses of mitochondrially synthesized proteins and mitochondrial DNA revealed that only mouse mitochondrial DNA was present in the hybrid lines. Thus, a nuclear coded mutation in human cells conferring resistance specifically to oligomycin and related ATPase inhibitors is expressed in interspecific human-rodent hybrid cells coincident with the retention of two chromosomes 10. It is likely that the ATPase of the hybrids contains both mouse and human subunits, since the hybrids retained and expressed only mouse mitochondrial DNA. (68 Refs)

44. INTRODUCTION OF A HUMAN X-6 TRANSLOCATION CHROMOSOME INTO A MOUSE TERATOCARCINOMA: INVESTIGATION OF CONTROL OF HLA-A,B,C EXPRESSION.

Goodfellow PN, Banting G, Trowsdale J, Chambers S, Solomon E
Imperial Cancer Res. Fund, Lincoln's Inn Fields, London, WC2A 3PX, England
Proc Natl Acad Sci USA; 79(4,part1):1190-1194 1982

We have developed an approach to human developmental biology which exploits somatic cell genetics. With this system we have examined the production of the HLA-A,B,C antigens. A human-mouse somatic cell hybrid was constructed which contained a human X-6 chromosome translocation carrying the HLA region; this hybrid was used as a donor of the X-6 translocation in the technique of microcell transfer. The X-6 chromosome recipient was the mouse embryonal carcinoma cell line PCC4. The microcell hybrid MCP-6 retained the embryonal carcinoma phenotype as judged by shape and absence of H-2 expression. Nonetheless, the expression of the HLA-A,B,C genes was not extinguished. HLA-A,B,C antigen production at the cell surface, however, was not detected because this hybrid apparently could not make B2-microglobulin. (Author abstract) (52 Refs)

45. ACTIVATION AND SUPPRESSION OF MELANOGENESIS IN MOUSE MELANOMA CELLS BY HYBRIDIZATION WITH CHICK EMBRYONIC CELLS.

Ishiguro SI, Takeuchi T
Biological Inst. and Dept. Biological Sciences, Tohoku Univ., Sendai 980, Japan
Dev Growth Differ; 23(2):185-189 1981

Sendai virus-induced fusion of 6-thioguanine resistant mouse melanoma cells (TG14) with chick embryo tissue (liver and neural retinal cells) resulted in hybrid cell formation. Differences in the ability of the embryonic tissue to affect melanogenesis was studied using tyrosinase activity and melanin content. Karyotypic analysis using the trypsin Giemsa method indicated isolated hybrid clones had retained an almost complete set of TG14 cell chromosomes, but lost most of the chick chromosomes. Values for tyrosinase activity and melanin content varied in hybrid clones; however, characteristic relationships between the two parameters were found in each type of fusion. Enhanced melanin production was observed in hybrids between slightly pigmented TG14 cells and retinal pigment cells; electrophoretic analysis of tyrosinase binding indicated mouse melanoma type. Electron micrographs revealed numerous Stage III and IV mouse melanoma type melanosomes in pigmented hybrid clones. Hybridization between melanoma cells and chick liver cells resulted in a decrease of tyrosinase activity, indicating suppression of melanogenesis. (29 Refs)

46. CARCINOEMBRYONIC ANTIGEN (CEA) EXPRESSION IN SOMATIC CELL HYBRIDS.

Sheer D, Brown RM, Bobrow M
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Somatic Cell Genet; 8(1):1-13 1982

Five intraspecific somatic cell hybrids formed between a human carcinoembryonic antigen (CEA)-producing colonic tumor cell line, LS174T, and a HeLa derivative that does not produce CEA, BU25.CAPR, were investigated for expression of CEA. The viable LSB clones (16, 20, 44, 45, and 46) all contained BU25.CAPR marker chromosomes; the clones all produced substantial CEA but less per cell than LS174T. The number of chromosomes lost in the hybrids compared with parental cells ranged from 3-17. Seven hybrid clones (LSPG) were formed between LS174T and the mouse melanoma cell line, PG19, and 28 hybrid clones (LSR) were formed between LS174T and the mouse kidney adenocarcinoma cell line RAG. The hybrids retained between 4 and 21 human chromosomes, and each human chromosome was represented in at least seven hybrids. Trace amounts of CEA were found in two hybrids, suggesting either repression of CEA production by the mouse genome or production of a structurally abnormal CEA molecule. (29 Refs)

MOLECULAR CYTOGENETICS

47. AMPLIFIED DNA SEQUENCES IN Y1 MOUSE ADRENAL TUMOR CELLS: ASSOCIATION WITH DOUBLE MINUTES AND LOCALIZATION TO A HOMOGENEOUSLY STAINING CHROMOSOMAL REGION.

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Proc Natl Acad Sci USA; 79(5):1597-1601 1982

DNA associated with double minutes (dm) of the Y1-DM mouse adrenocortical tumor cell line has been cloned in Charon 4A and a preliminary characterization has been made of a recombinant clone, lambdaY1dm-1, isolated from this dm DNA library. Cloned sequences in lambdaY1dm-1 are amplified in the genome of the Y1-DM cells. They are also amplified in the genome of a related Y1 subline (Y1-HSR), which has a homogeneously staining chromosomal region (HSR). Here we report that the amplified sequences complementary to lambdaY1dm-1 are localized to the HSR, as determined by in situ hybridization. In addition, we found that a population of Y1-DM cells originally containing only dm later consisted of two cell types. Some cells retained dm; others had lost dm but gained a HSR-bearing chromosome morphologically distinct from that in the Y1-HSR cell line. Subclones isolated from this mixed culture have either dm or a HSR, but not both. Southern blotting studies revealed that genomic DNA samples from subclones with a HSR, like subclones with dm, still possess amplified copies of DNA homologous to our recombinant probe. These experiments provide direct evidence that the dm and HSRs in these Y1 cells are structurally related and further support the hypothesis that these chromosomal anomalies result from a process of gene amplification. (Author abstract) (25 Refs)

48. CHROMOSOME STRUCTURE AND DNA SEQUENCE ALTERATIONS ASSOCIATED WITH MUTATION OF TRANSFORMED GENES.

Robins DM, Axel R, Henderson AS
Inst. Cancer Res., Coll. Physicians and Surgeons, Columbia Univ., 701 West 168th St., New York, NY, 10032
J Mol Appl Genet; 1(3):191-203 1981

Four well-characterized transformed BRL rat liver cell lines, containing the viral tk gene (tk+) and 5-10 human growth hormone (HGH) sequences, and revertant sublines lacking the tk gene (tk-), were analyzed for the presence of tk and HGH sequences by blot hybridization to restriction endonuclease-cleaved DNA. Some of the tk- revertants were also characterized by karyotypic analysis and hybridization in situ. Over 50% of 40 tk- revertants had deleted all of the transforming DNA from the recipient chromosome. In 15 other revertants, a significant amount of deletion was observed but some of the transforming DNA was retained. The deletion of transforming DNA was never associated with the loss of an entire chromosome. In this restricted set of mutants, it seemed to be crucial to maintain a diploid chromosomal complement. This condition might be required for the survival of somatic cells in which essential genes are often present in a functionally hemizygous state. Alternatively, subtle gene dosage effects might require a balance associated with diploidy. (18 Refs)

49. MURINE ERYTHROLEUKEMIA CELL DIFFERENTIATION: DNASE I HYPERSENSITIVITY AND DNA METHYLATION NEAR THE GLOBIN GENES.

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Proc Natl Acad Sci USA; 79(4,part1):1180-1184 1982

The sensitivity to digestion by DNase I of chromatin containing the alpha- and betamajor-globin genes and the pattern of DNA methylation near these genes was examined during hexamethylenebisacetamide (HMBA)-mediated erythroid differentiation of murine erythroleukemia cells (MELC). In uninduced and induced cells, the chromatin regions containing the alpha- and betamajor-globin genes are more sensitive to digestion by DNase I than is the region containing an immunoglobulin gene (Igalpha) not expressed during erythroid differentiation. However, at low concentrations of DNase I, a 6-to 10-fold increase in site-specific cleavages was generated in chromatin regions near both the alpha- and betamajor-globin genes in cells induced to differentiate by HMBA. The DNase I hypersensitive site near the betamajor-globin gene maps to a small region near the 5' terminus of the gene. No detectable change in the pattern of DNA methylation around either the alpha- or beta-globin genes was observed during HMBA-mediated erythroid differentiation. Of the potentially methylated sites assayed and mapped near the betamajor-globin gene, one site is fully methylated, one is partially methylated, and one is unmethylated both in uninduced and induced cells. Many (but not all) sites assayed near the alpha-globin genes are unmethylated in both uninduced and induced cells. These results show that specific alterations of chromatin structure occur during MELC differentiation and suggest that these changes may not involve alterations in the pattern of DNA methylation. (Author abstract) (35 Refs)

50. GENOME INSTABILITY IN A REGION OF HUMAN DNA ENRICHED IN ALU REPEAT SEQUENCES.

Calabretta B, Robberson DL, Barrera-Saldana HA, Lambrou TP, Saunders GF

Dept. Biochemistry, Univ. Texas System Cancer Center, Houston, TX, 77030

Nature; 296(5854):219-225 1982

DNA rearrangements involving restriction fragment length polymorphism and variation in copy number were detected in the human genome by blot hybridization with a cloned segment of human DNA initially present in a cluster of Alu repeat sequences. These rearrangements involve both extrachromosomal circular duplex DNAs and integrated sequences, indicating the presence of transposable elements in human cells. (Author abstract) (29 Refs)

EFFECTS OF EXOGENOUS AGENTS ON CHROMOSOMES

51. DIFFERENTIAL PERSISTENCE OF CHROMOSOMAL DAMAGE INDUCED IN RESTING RAT-LIVER CELLS BY X-RAYS AND 4.2-MEV NEUTRONS.

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Mutat Res; 92(1/2):275-290 1982

Young male Wistar rats (35-45 days old) or mature WAG/Rij female rats (24 wk old) were exposed to total-body irradiation with x-rays (XR: 100-400 rads) or 4.2 million electron volt neutrons (NR: 25-100 rads). Partial hepatectomy was performed 1 day-3 mo after irradiation; 2-3 days postoperatively, the remaining liver was perfused and isolated hepatocytes were examined for cytoplasmic micronuclei. Both XR and NR caused a dose-related increase in the occurrence of micronuclei. The plateau of the dose-effect curve was observed at 400 rads XR and 50 rads NR. In the XR group, the frequency of micronucleated hepatocytes decreased with increasing time intervals after irradiation; the frequency at 3 mo was not significantly different from the control value. In the NR group, the frequencies of micronucleated hepatocytes remained constant at all time intervals studied. The progressive decline in the frequencies of hepatocytic micronuclei after XR exposure may be explained by two mechanisms operating simultaneously: slow, long-term repair of chromosomal damage and mitotic selection against cells bearing substantial amounts of chromosomal damage. The mechanisms did not seem to be in effect in the NR group. The relative biologic effectiveness of NR in the ascending portion of its dose-effect curve was about 4 relative to XR. The long-term effects of XR and NR should be compared at lower doses, at which cell regeneration induced by XR is not demonstrable. Such experiments might provide more information on possible long-term repair processes in resting (GO) liver cells with XR-induced chromosomal damage. (26 Refs)

52. A COMPARATIVE STUDY OF THE RELATIVE FREQUENCY AND SPECIFIC PATTERN OF CHROMATID INTERCHANGES INDUCED BY MONO-, DI- AND POLY-FUNCTIONAL ALKYLATING AGENTS.

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Mutat Res; 104(1-3):153-158 1982

The ability to distinguish among the actions of different classes of alkylating agents by characteristics of chromatid exchange (frequency with which a chromosome region takes part in an interchange and frequency with which the region exchanges with other chromosome regions) was examined in lymphocytes taken from a marsupial hybrid (Macropus rufogriseus female x Wallabia bicolor male). The hybrid has one genome of eight chromosomes from M rufogriseus, each of which has substantial C-banding centrometric heterchromatin, while the chromosomes of the W bicolor genome have virtually none. Data from a previous mitomycin C experiment (final concentration 3 x 10(-7) M) were compared with data obtained following treatment with the monofunctional alkylating agent methanesulfonate (4 x 107-6 M) and the polyfunctional agent trenimon (3 x 10(-7) M). No difference in relative frequency with which a chromosome region was involved in an interchange after treatment with the three agents was observed. A further analysis made of the spe cific pattern of interchanges produced by the three agents using the likelihood ratio test of equality of proportions showed no evidence of a difference in the specific pattern of interchanges produced by the three agents. (9 Refs)

53. CELL INJURY AND DNA REPAIR IN X- AND NEUTRON-IRRADIATED CHINESE HAMSTER CELLS.

Korner IJ, Tolkendorf E, Handschack W, Malz W
Central Inst. Molecular Biology, Acad. Sciences GDR, Lindenberger Weg 70, DDR-1115 Berlin, E. Germany
Stud Biophys; 86(1):81-82 1981

Survival rates and chromosome aberrations under oxic and hypoxic conditions and DNA single- and double-strand break rejoining in x- and neutron-irradiated Chinese hamster cells under oxic conditions were investigated. Relative biological effectiveness (RBE) decreased with increasing neutron dose. Survival curves provided an oxygen enhancement ratio of approx 3.0 after x- and 1.9 after neutron-irradiation. The results of chromosome aberrations induction provided the highest RBE for asymmetrical chromosomal exchanges dependent on neutron dose. The higher RBE of the fast neutrons concerning the survival correlated with the rate of chromosome breaks and DNA double-strand breaks and also with a decreased rejoining of single- and double-strand breaks. (5 Refs)

54. INDUCTION OF CHROMATID BREAKAGE BY CLASTOGENS IN CELLS OF G2 PHASE.

Hsu TC, Cherry LM, Pathak S
Dept. Cell Biology, Univ. Texas M. D. Anderson Hosp. and Tumor Inst. at Houston, Houston, TX, 77030
Mutat Res; 93(1):185-193 1982

Clastogenicity of several compounds was tested in cultures of human peripheral blood cells in G2 phase. Cells were exposed simultaneously to Colcemid and actinomycin D (AMD: 2.8 uM for 15, 30, 45, or 60 min or 2.8, 1.4 or 0.28 uM for 60 min). Chromosome breakage was induced in a dose-dependent manner. The most frequent aberrations were chromatid breaks; chromatid exchanges were rare. In a modified procedure, cells were exposed to 2.8 uM AMD for 90 min, but to Colcemid for only the last 60 min. Among 100 metaphase figures 95% had chromatid breaks; the av number of breaks/cell was 3.77. Autoradiographic studies indicated that all chromatid aberrations occurred during G2 phase. Additional clastogens were tested at 100 uM concentrations (or at lower concentrations when 100 uM was too toxic). Chromatid breaks were produced by adriamycin, bleomycin, neutral red, gentian violet, and 1,4-dihydroxy-5,8- [*2-(2 hydroxymethyl)amino*]*ethylamino* -9,10-anthracenedione at 15-100x the frequency produced in controls. No increases in the frequency of chromatid breaks were produced by mitomycin C, hydroxyurea, ethidium bromide, or cytosine arabinoside. Cis-platinum II produced borderline results. N-Methyl-N'-nitrosoguanidine was mildly clastogenic in G2 phase. Results indicate that a simple protocol can be used to determine clastogenicity in G2-phase cells. (8 Refs)

55. THE RELATIONSHIP BETWEEN DNA AND CHROMOSOME DAMAGE AFTER BLEOMYCIN TREATMENT: DOSE-RESPONSE MEASUREMENTS.

Sognier MA, Hittelman WN, Pollard M
Dept. Developmental Therapeutics, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Mutat Res; 93(1):149-159 1982

Formation of chromosomal aberrations (CA) was studied in Chinese hamster ovary cells exposed to bleomycin in various concentrations and for various exposure times. Curves of alkaline elution of DNA and CA (as measured by G2 premature condensation of chromosomes) showed a two-compartment response with a more sensitive compartment at low doses. The two-compartment response was less evident when CA was enumerated in mitotic figures, suggesting that cellular chromatin determines sensitivity to bleomycin. Use of different doses and times to produce equivalent DNA damage indicated that rapidly repaired DNA lesions are not involved in chromatid exchanges. (24 Refs)

56. CYTOGENETIC ANALYSIS OF MOUSE BONE MARROW RADIOPROTECTION WITH INTERFERON INDUCER POLY-I-POLY-C.

Zhukova NA, Palyga GF, Maksimenko AA, Zavitaeva TA

Res. Inst. Medical Radiology, Obninsk, USSR

Stud Biophys; 86(3):205-210 1981

The radioprotective effect of interferon inducer poly I-C was studied in male (CBA x C57BL)F1 mice. Animals were subjected to whole-body gamma irradiation with 100, 200, and 400 rads; 48 hr prior to irradiation, animals were injected ip with poly I-C (0.2 ml). Prophylaxis administration of poly I-C reduced the incidence of chromosome aberrations in the bone marrow of irradiated mice. The most pronounced decrease of the frequency of chromosome and chromatid aberrations was observed after irradiation with 400 rads. (11 Refs) (In RUS)

57. EFFECTS OF AMPHIDICOLIN ON REPAIR REPLICATION AND INDUCED CHROMOSOMAL ABERRATIONS IN MAMMALIAN CELLS.

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Mutat Res; 92(1/2):379-392 1982

In growing cultures of normal human skin fibroblasts (HF) and HeLa cells, aphidicolin (APH: 5 ug/ml) enhanced DNA repair replication after UV exposure. In confluent HF cultures, APH inhibited UV-induced repair replication. This inhibitory effect was enhanced in the presence of hydroxyurea (HU: 10 milliM). In confluent HeLa cell cultures, APH inhibited UV-induced repair replication in the presence of HU but enhanced it in the absence of HU. In x-irradiated human peripheral blood lymphocytes (PBL), APH exposure during the G0 or G1 phase increased the occurrence of chromosome breaks and exchanges. The effects of APH on the induction of chromosomal damage in Chinese hamster ovary (CHO) cells depended on the cell cycle stage. In synchronized CHO cells, APH did not significantly affect the frequencies of chromosomal aberrations induced by exposure to x-rays during G2. In G2 cells, APH enhanced the frequencies of x-ray-induced chromatid breaks. In CHO cells exposed to UV, mitomycin C, monofunctional mitomycin C, or 4-nitroquinoline 1-oxide during G1 and exposed to APH in G2 (just before fixation), the frequencies of chromosomal aberrations were higher than in cells exposed only to UV or the alkylating agents. Despite the difficulty of making direct comparisons between the effects of APH on DNA-repair replication and the frequencies of induced chromosomal aberrations, these results indicate that cell type and cell cycle stage influence the biologic responses to APH. (18 Refs)

58. CYTOGENETIC EFFECTS OF EPOXY, PHENOLFORMALDEHYDE, AND POLYVINYLCHLORIDE RESINS IN MAN.

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Mutat Res; 104(1-3):137-140 1982

Cytogenetic effects of synthetic resins were studied in workers exposed to epoxy and polyvinylchloride (PVC) in the manufacture of goods or to phenol and formaldehyde in the production of phenolformaldehyde (PF) resins. Chromosomal aberrations (CA) were analyzed in peripheral lymphocytes from resin workers (av age 39.1 yr, exposure 4 mo-30 yr) and healthy nonexposed controls. Exposure to the synthetic resins and their components was by inhalation and skin exposure. Av concentration of chemical in the air was 6 mg/cubic meter (m3) for vinyl chloride, 1 mg/m3 for epichlorohydrin (a component of epoxy resin), 0.3 mg/m3 for phenol, and 0.5 mg/m3 for formaldehyde. Among controls CA were found in 2.4% of cells; 0.024 aberrant chromosomes (AC)/cell were found; 1.26 breaks/chromosomes were found. The frequency of CA in cells from exposed workers was 5.5% for epoxy resin, 6.1% for PVC, and 5.0% for PF. Significant increases in AC/cell were found for all compounds. A significant increase in chromosomal breaks/cell was found only for PVC. Acentric single and paired chromosomal fragments were the predominant aberration noted, accounting for 90%. Results indicate the need for further study of the hazards of occupational exposure to synthetic resins and components of the resins. (5 Refs)

59. METRIFONATE AND DICHLORVOS: CYTOGENETIC INVESTIGATIONS.

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Dept. Genetics, Univ. Liege, B-4000 Liege, Belgium
Acta Pharmacol Toxicol [Suppl] (Copenh); 49(5):29-39 1981

Contradictory results are found in the literature about the cytogenetical effects of dichlorvos and metrifonate in mammals whereas their chromosome breaking ability was demonstrated in plant and Drosophila cells. They were tested on both in vitro and in vivo cells for chromosome breakage. Dominant lethal mutations were also investigated in mouse as well as epidemiological studies in man. In our experiments on mouse bone marrow and testis, one acute dose was injected respectively: 10 mg/kg for dichlorvos and 100 mg/kg for metrifonate. These experiments failed to reveal any clastogenic effect in these test systems as well as in chronic treatments respectively 2 ppm/5 days a wk for 7 wk for dichlorvos and 0.5 ppm 5 days a wk for 7 wk for metrifonate. In an investigation of dominant lethal mutations, dichlorvos did not enhance the frequency of dead embryos but the frequency of pre-implantation losses was significantly increased in two specific periods of the seven investigated. In the same test, metrifonate did not produce any effect. These data are compared with those obtained with trimethylphosphate and MMS taken as positive controls. These results will serve to reevaluate the cytogenetical risks of dichlorvos and metrifonate. (Author abstract) (36 Refs)

60. CYTOGENETIC EFFECTS OF LEAD AND CADMIUM COMPOUNDS ON ASCITIC TUMOUR CELLS IN THE MOUSE.

Bishun N, Pentecost M
Tissue Culture and Cytogenetics Unit, Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey, Great Britain
Microbios Lett; 17(65):29-32 1981

The chromosomal effects of cadmium and lead compounds on ascitic tumor cells grown in vivo in mice, were investigated. Lead nitrate was shown to cause chromosomal damage but a dose response relationship was not established. Furthermore, cadmium sulfate was shown to be ineffective as a clastogenic compound. (Author abstract) (4 Refs)

61. EFFECT OF CEPHALORIDINE ON HUMAN CHROMOSOMES IN VITRO IN LYMPHOCYTE CULTURES.

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Mutat Res; 101(1):57-66 1982

The clastogenic effect of cephaloridine (CEP; antibiotic derived from cephalosporin C) on human chromosomes was investigated in vitro in WBC cultures. CEP was added to 72-hr cultured cells in concentrations of 10, 20, 60, and 120 ug/ml for 24, 48, or 72 hr. Two concentrations of CEP (20 and 60 ug/ml) were similar to those found in the plasma of persons given therapeutic doses of 500 mg and 2 g, respectively. The 10 ug/ml dose was below and the 120 mg dose was above plasma levels. Chromosome aberration frequency increased with increasing dose: 3.3% with 10 ug/ml, 4.2% with 20 ug/ml, 10.25% with 60 ug/ml, and 22.84% with 120 ug/ml. No significant chromosomal damage was produced by 10 and 20 mg CEP/ml. At 60 and 120 ug/ml, a significant increase in chromosomal damage was noted and the frequency of aberrations was higher in cells exposed during the last 24 hr compared with 48-hr and 72-hr treatments. Chromosome Group A, B, and C contained more aberrations than did chromosomes D, E, and F; groups G and Y were not affected. Aberrations were mostly of the chromatid type. Thus, CEP is clastogenic at the upper levels of permissible therapeutic doses. (13 Refs)

62. A COMPARISON OF INDUCED SISTER CHROMATID EXCHANGE LEVELS IN CHINESE HAMSTER OVARY CELLS AND CULTURED HUMAN LYMPHOCYTES.

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Environ Mutagen; 4(1):65-71 1982

The effects of six DNA damaging agents on the induced sister chromatid exchange (SCE) rate were compared in peripheral blood lymphocytes from healthy human subjects and Chinese hamster ovary (CHO) cells. Both types of cells were exposed to two cycles of each agent. Differential staining of SCE was by a slight modification of the method of Perry and Wolf. Dunnett's test for multiple comparison was used to determine which treatment groups differed from controls. Significantly increased SCE levels were observed in CHO cells after 5-bromodeoxyuridine (50 ug/ml), proflavine (0.2 and 0.5 ug/ml), bleomycin (2.0-6.0 ug/ml), vincristine (0.05-1.00 ug/ml), and 3H-uridine (0.37 and 3.70 kBq/ml). SCE levels of human lymphocytes were only increased by 5-bromodeoxyuridine, proflavine, and the highest dose of 3H-uridine. Colcemid did not increase SCE in either cell system. It is suggested that SCE analysis in response to mutagens and carcinogens should be based on more than one cell type. (26 Refs)

63. 12-O-TETRADECANOYL-PHORBOL-13-ACETATE AND ITS RELATIONSHIP TO SCE INDUCTION IN SYRIAN AND CHINESE HAMSTER CELLS.

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Environ Mutagen; 4(1):73-81 1982

Alteration of cell culture conditions, 12-O-tetradecanoyl-phorbol-13-acetate (TPA), or 5-bromodeoxyuridine (BUdR) concentrations, or temporal relation between UV or x-irradiation and TPA had no effect on sister chromatid exchange (SCE) induction of Syrian hamster embryo cells (HEC). SCE frequencies were determined on exponentially growing and stationary HEC cultures incubated with different BUdR concentrations for one or two replicative cycles. TPA (0.01-2.0 ug/ml medium) was ineffective in inducing SCE in HEC cultures cultivated in medium supplemented with heat-inactivated serum, independent of BUdR concentration (1.0-10.0 ug/ml) and the number of cell divisions post treatment. In a similar study, TPA did not increase SCE frequency in V79-4 Chinese hamster cells in heat-inactivated or noninactivated serum. TPA has no effect on UV or x-irradiation induced SCE. X-irradiation (200 R) causes an increase of only 1 SCE/cell over the control value, while UV (1.5 and 3.0 J/square meter) causes an increase of 10 and 24 SCE per metaphase. TPA addition either immediately or 48 hr after UV or x-irradiation did not alter SCE frequency obtained by irradiation alone. Although SCE induction may be important for the induction of transformation by environmental agents, the enhancement of transformation frequency caused by TPA occurs without further DNA alterations involved in SCE formation. (21 Refs)

64. 12-O-TETRADECANOYLPHORBOL-13-ACETATE (TPA) INDUCES SISTER-CHROMATID EXCHANGES AND DELAYS IN CELL PROGRESSION IN CHINESE HAMSTER OVARY AND HUMAN CELL LINES.

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Mutat Res; 92(1/2):393-409 1982

In Chinese hamster ovary (CHO) cells and SV40-transformed human fibroblast cell lines (GM637 and XP12RO), 12-O-tetradecanoylphorbol-13-acetate (TPA: 1.0 nanog-1.0 ug/ml) caused a 20-45% increase in the frequency of sister chromatid exchanges (SCEs). This increase in SCEs was not caused by an impurity in the TPA preparation, or increased 5-bromo-2'-deoxyuridine uptake into DNA; it was independent of the incubation time between TPA exposure and fixation of the cells. Simultaneous exposure to TPA (1.0 ug/ml) and benzo(a)pyrene (BP: 1.7 x 10(-5)-3.3 x 10(-6) M) led to a synergistic SCE induction in CHO cells. No synergism was observed after simultaneous exposure to TPA (1 ug/ml) and mitomycin C (0.03 ug/ml) or UV light. In addition to its weak SCE-inducing effects in CHO cells, TPA alone caused a slight delay in cell cycle progression and markedly enhanced the cell cycle delay induced by BP. The SCE-inducing capacity of TPA in these cells was unrelated to its toxicity, because TPA was not toxic at the doses used. It also seemed to be unrelated to excision repair capacity, because TPA caused similar increases in SCE frequency in cells which were proficient (GM637), mildly deficient (CHO), and severely deficient (XP12RO) in excision repair. The significance of SCE induction and its relationship to other biologic effects of TPA remain unknown. (40 Refs)

65. 5-BROMODEOXYURIDINE TABLETS WITH IMPROVED DEPOT EFFECT FOR ANALYSIS IN VIVO OF SITER-CHROMATID EXCHANGES IN BONE-MARROW AND SPERMATOGONIAL CELLS.

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Mutat Res; 97(2):117-129 1982

Uncoated and agar-coated tablets of 5-bromodeoxyuridine (BUdR; 50 mg) were implanted sc into NMRI mice. Compared to the uncoated tablets, agar-coated tablets provided a slower, more uniform delivery of BUdR. The slow dissolution rate of the agar-coated tablets permitted a reduction of the BUdR doses for assays of sister chromatid exchanges (SCE) in the bone marrow, thereby reducing undesired effects of high BUdR doses on the baseline SCE frequency as well as on cellular replication and proliferation. The agar-coated tablets could also be used to study SCE figures in the spermatogonia. (31 Refs)

66. THE INDUCTION OF SPECIFIC-LOCUS MUTATIONS AND SISTER-CHROMATID EXCHANGES BY 5-BROMO- AND 5-CHLORO-DEOXYURIDINE.

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Mutat Res; 92(1/2):411-416 1982

Chinese hamster ovary (CHO) cells were incubated for 25-32 hr with 5-bromo-2'-deoxyuridine (BUdR) or 5-chloro-2'-deoxyuridine. (ClUdR). Over the entire concentration range from 0.5-200 uM, both agents caused a dose-dependent increase in sister chromatid exchanges (SCEs) in the CHO cells. ClUdR induced 3-5x more SCEs than BUdR at the same concentration. Since ClUdR and BUdR showed similar levels of cytotoxicity and were incorporated into DNA to similar extents at a given concentration, the greater SCE-inducing capacity of ClUdR was attributed to the nature of the halogen substitution. Both agents (especially ClUdR) induced a high frequency of chromosome aberrations at greater than 100 uM. Both agents induced mutations to 6-thioguanine resistance (TGr) at greater than 50 uM. BUdR was consistently more mutagenic than ClUdR at the same concentration. Highly mutagenic concentrations of BUdR induced far fewer SCEs than induced by nonmutagenic concentrations of ClUdR. It is concluded that the mutagenic effects of BUdR and ClUdR are distinct from their SCE-inducing activities. These findings cast doubt on the practice of predicting mutation induction from studies designed to measure SCE frequency. (13 Refs)

67. SISTER-CHROMATID EXCHANGE (SCE) ANALYSIS IN MOTHERS EXPOSED TO DNA-DAMAGING AGENTS AND THEIR NEWBORN INFANTS.

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Mutat Res; 97(2):139-146 1982

Sister chromatid exchange (SCE) frequencies in the peripheral blood lymphocytes were studied in several groups of adults (17-43 yr old): 20 healthy nonsmokers, 30 nonsmoking mothers (studied during the postpartum period), 23 mothers who had smoked during pregnancy (5-15+ cigarettes/day), 9 mothers who had abused alcohol during pregnancy (all were heavy smokers and some had histories of intake of marijuana, lysergic acid diethylamide, and other narcotics); and 13 mothers with chronic illness (3/13 had malignancies but no radiotherapy or chemotherapy during pregnancy). The infants of all mothers were clinically normal. SCE frequencies were also studied in 19 healthy children (1-10 yr old) and three groups of abnormal infants having multiple congenital malformation (MCM: 26), neural tube defect (NTD: 24), or Down's syndrome (DS: 13). The normal newborn infants showed significantly lower SCE frequencies than the older children and adults. The women who abused alcohol during pregnancy showed significantly higher SCE freque ncies than the control mothers, but the smoking mothers did not. None of the maternal habits significantly affected the SCE frequencies in the infants. One of the women with chronic disease (multiple sclerosis) showed an elevated SCE frequency. The SCE frequency in her infant was not studied. Two infants whose mothers had chronic diseases (Hodgkin's disease or anticonvulsant-treated epilepsy) showed elevated SCE frequencies, but their mothers did not. Among the abnormal infants, NTD was associated with elevated SCE frequencies, but MCM and DS were not. Not all of the mothers of abnormal infants were studied, but the available evidence indicated no elevated SCE frequencies or material exposure to DNA-damaging agents exceeding that observed in the control group. (24 Refs)

68. INDUCTION OF SISTER CHROMATID EXCHANGE BY POLYOMA LARGE VIRAL TUMOR ANTIGEN IN TRANSFORMED RAT FIBROBLASTS.

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Cancer Res; 42(5):1909-1912 1982

The frequency of sister chromatid exchange (SCE) was determined in rat fibroblasts transformed by wild-type polyoma virus or by a mutant temperature sensitive for viral large tumor antigen function (ts-a). Elevated SCE frequencies were observed in two wild-type transformed cell lines growing at 37 C and in four ts-a-transformed lines upon growth at the permissive temperature for large viral tumor antigen (33 C). The increase in SCE frequency in ts-a-transformed cells at 33 C was reversed by growth at 39 C (nonpermissive for T-antigen function). An increase in SCE at 33 C was not observed in untransformed cells or in a ts-a-transformed cell line which makes a defective large viral tumor antigen. These results suggest that large viral tumor antigen can induce SCEs. Since large viral tumor antigen is also responsible for amplification of integrated viral DNA sequences (4), we tried to correlate this phenomenon with the increased SCE frequency. However, increasing SCE artificially by growing cells in the presence of 12-O-tetradecanoylphorbol-13-acetate did not result in amplification of integrated viral DNA in the absence of large viral tumor antigen function. Thus, there is no simple causal relationship between increased SCE and amplification. (Author abstract) (18 Refs)

69. GENOTOXIC ACTIVITY OF FIVE ANTIDEPRESSANT HYDRAZINES IN A BATTERY OF IN VIVO AND IN VITRO SHORT TERM TESTS.

Brambilla G, Cavanna M, Faggin P, Pino A, Robbiano L, Bennicelli C, Zanacchi P, Camoirano A, De Flora S
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J Toxicol Environ Health; 9(2):287-303 1982

The mutagenic and potential carcinogenic activity of iproniazid (IPZ), phenelzine (PHZ), nialamide (NLM), isocarboxazid (ICB), and mebanazine (MBZ) was assessed. Mouse liver and lung DNA damage was analyzed by the alkaline elution technique after single or daily, ip or po doses of each drug, ranging from 0.333 to 2x the LD50. ICB, NLM, PHZ, and MBZ caused significant DNA fragmentation with decreasing efficiency, while IPZ was ineffective. In contrast to ICB, NLM, and PHZ, MBZ induced DNA damage only in the lung and only after five successive daily doses. Sister chromatid exchange (SCE) in mouse bone marrow cells was assessed after ip administration of 1-2x the LD50 of each drug except MBZ. SCE frequencies in the IPZ, NLM, ISB, and PHZ treated groups increased 71%, 49%, 46%, and 34%, respectively, when compared with control groups. A dose-dependent increase in SCE frequency was observed in mice treated with ICB at LD50 and 2x LD50. Mutagenic activity was investigated with the Salmonella/microsome test. NLM and PHZ were mutagenic in the spot test (1 mg/plate) and the plate incorporation test (PIT). ICB and IPZ were not mutagenic, and MBZ was weakly mutagenic in the PIT. Antibacterial activity in repair deficient Escherichia coli was also assessed for each compound. ICB and IPZ were scarcely toxic, while NLM, PHZ, and MBZ showed significantly increased antibacterial activity in some E coli strains with spot and spiral tests. Long term carcinogenic tests should be performed for NLM and ICB, which are still in clinical use. (30 Refs)

70. INCREASED INDUCTION OF SISTER CHROMATID EXCHANGE BY DIETHYLSTILBESTROL IN LYMPHOCYTES FROM PREGNANT AND PREMENOPAUSAL WOMEN.

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Cancer Res; 42(3):893-896 1982

Cultures of whole blood from pregnant women (4 to 6 mo), premenopausal women, postmenopausal women, and normal men were grown in the presence of varying concentrations (1 x 10(-5) M, 2 x 10(-5) M, and 4 x 10(-5) M) of diethylstilbestrol (DES), a synthetic estrogen and known carcinogen, to see if it had sex-related cytogenetic effects. DES induced sister chromatid exchanges in lymphocytes from pregnant and premenopausal women but had only a small effect at the highest concentration (4 x 10(-5) M) in lymphocytes from men and postmenopausal women. At all concentrations, the av number of sister chromatid exchanges was higher in lymphocytes from pregnant women than in those from premenopausal women. In lymphocytes from both a man and a pregnant woman, DES strongly inhibited cell proliferation in vitro. When lymphocytes from a man and a pregnant woman were cocultured in the presence of DES, only the lymphocytes of the woman responded with an increase in sister chromatid exchanges. This indicated that there is no interaction between DES and a factor present in the blood but that DES acts directly on each cell. (Author abstract) (24 Refs)

71. SISTER-CHROMATID EXCHANGE INDUCTION BY CIS-PLATINUM/ADRIAMYCIN CANCER CHEMOTHERAPY.

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Mutat Res; 104(1-3):131-136 1982

Induction of sister-chromatid exchanges (SCE) by chemotherapy with cis-platinum (cis-DDP) and adriamycin (ADM) was studied in five patients (3 men and 2 women, 55-72 yr old) with advanced metastatic cancer. Tumors included adenocarcinoma of the ovary (Stage III), carcinosarcoma of the endometrium, transitional cell carcinoma of the bladder (Stage IV, 2 cases), and epidermoid cancer of the head and neck. All patients had undergone previous chemotherapy at varying intervals prior to the study. SCE and chromosomal aberrations (CA) were measured in cultures of peripheral lymphocytes obtained 1 mo after a course of chemotherapy or 5 hr after iv infusion of cis-DDP (100-110 mg) and ADM (100-110 mg). Twenty-two patients with solid tumors sampled before therapy served as controls. Cells were incubated for 72 hr. CA grade included chromatid and isochromatid breaks, acentric fragments, rings, dicentrics, and exchange figures. The frequency of SCE was similar in untreated patients (7.57 +-0.83 SCE/cell) and noncancer controls (6.92 +-0.80 SCE/cell). Pretreatment frequencies were higher (10.05 +-2.54 SCE/cell) in the test patients, probably due to effects of prior chemotherapy. Cultures of cells collected 5 hr after treatment showed 18.97 +-1.97 SCE/cell. Two test patients had normal SCE values 1 mo after prior chemotherapy. CA were found in 7.0 +-5.2% of cells. SCE provided a better index of mutagenic exposure than CA. Results indicate short-term mutagenic effects of chemotherapy with cis-DDP and ADM. (9 Refs)

72. INDUCIBILITY OF SISTER-CHROMATID EXCHANGES BY HEAVY-METAL IONS.

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Mutat Res; 104(1-3):141-145 1982

Induction of sister-chromatid exchanges (SCE) by heavy metal ions was studied in Don Chinese hamster (DCH) cells in vitro. In each test 4 x 10(4) cells were incubated for 72 hr with 1 ml growth medium and a particular concentration of metallic compound. Cultures were exposed to 5-bromo-2'-deoxyuridine (BUdR) for two cell cycles (28 hr). Metal ions tested included Ti+++, Cr+++, Cr++++++, Fe++, Fe+++, Ni++, As+++, As+++++, Se++, Cd++, Sn++, and Hg++. Metallic compounds were dissolved in dimethyl sulfoxide. Median tissue culture inhibition doses (TCID50) were calculated by microscopic examination of fixed, stained cells. Rates of SCE were calculated for the TCID50 of each test ion. Spontaneous SCE occurred in untreated control cells at a rate of 3.90 +-0.82 SCE/metaphase. Any result greater than 5.4 SCE was considered to be a significant increase. Significant increases were produced by Cr+++, Cr++++++, Ni++, As+++, and As+++++. Cr++++++ produced a greater increase in SCE than did Cr+++. As+++ produced a greater increase in SCE than did As+++++. Although Se++ is a suspected carcinogen, increased SCE were not produced at TCID50. (17 Refs)

73. INCIDENCE OF NICKEL-INDUCED SISTER-CHROMATID EXCHANGE.

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Mutat Res; 101(1):67-75 1982

The incidence of nickel-induced sister-chromatid exchange (SCE) was studied in cultured human peripheral blood lymphocytes from a single donor. Nickelous chloride was added to cultures to a final concentration of 10(-3) to 10(-6) M. Control cells had a mean background incidence of 3.92 +-0.7 (standard error) SCE/cell. Addition of 1.19 x 10(-4) M nickel approx doubled the SCE incidence to 8.52 +-0.33 SCE/cell. Concentrations of nickel less than 1 x 10(-4) M yielded SCE values between 8.52 and 3.92/cell. Concentrations of 5 x 10(-4) M or more were lethal to human peripheral WBC. Chi-square analysis of the nickel response for variation in location of activity across the karyotype revealed no differences. More SCE were found in chromosomes 1 and 2 and those of Group B while fewer SCE were found in Group E, F, and G. The increased SCE frequency induced by nickel was statistically significant at the 99% confidence level and appeared to be of the same order of magnitude as chromium in Chinese hamster ovary cells. (20 Refs)

74. CYTOGENETIC EFFECTS OF TWO ANTIMONIAL ANTIBILHARZIAL DRUGS: TARTAR EMETIC AND BILHARCID.

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Environ Mutagen; 4(1):83-91 1982

The effect of tartaric emetic (TE) and bilharcid (BH) on chromosomes of bone marrow was studied in rats. Both drugs were given ip, at three dose levels, clinical usage, intermediate, and maximum tolerated dose. These doses are 2.0, 8.4, 14.8 mg/kg for TE, and 1.0, 10.0, 19.1 for BH. Each dose was studied both acutely (6, 24 and 48 hr after a single injection) or subacutely where drug was given daily for 5 consecutive days, with sacrifice 6 hr after the last dose. Both drugs induced the same types of chromosomal aberrations (chromatid gaps and breaks, and centric fusions), with a higher incidence due to TE. No isochromatid gaps or breaks, or exchange figures were observed. No significant differences in number of cells with chromosomal aberrations were noted after the acute treatment (6, 24, 48 hr) with both drugs. The dose-response was examined for both acute and subacute treatments. There was a dose-response relationship for the treatment with TE. Maximum effects with subacute TE and acute and subacute BH were obtained at an intermedi ate dose. (15 Refs)

75. GENETIC DAMAGE CAUSED BY METHYLAZOXYMETHANOL ACETATE, THE AGYLCONE OF CYCASIN. ANALYSIS OF SISTER-CHROMATID EXCHANGE FREQUENCY UNDER IN VIVO CONDITIONS AND IN CELL CULTURES.

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Oncology; 39(2):101-103 1982

To extend the information on the mutagenic effect of methylazoxymethanol (MAM) acetate, which has been established as a potent carcinogen, the frequency of sister-chromatid exchange (SCE) was determined in bone marrow cells of Sprague Dawley rats and in cultured rat lymphocytes. To get differentially stained chromatids under in vivo conditions, the rats received 5-bromodeoxyuridine adsorbed on activated charcoal intraperitoneally. Chromosomes were stained with fluorescence plus Giemsa. In this study a significant increase of SCE frequency after the application of various concentrations of MAM acetate could be observed both in vivo and in vitro. (Author abstract) (20 Refs)

76. SISTER-CHROMATID EXCHANGE AND CHROMOSOMAL ABERRATIONS BY DHAQ AND RELATED ANTHRAQUINONE DERIVATIVES IN CHINESE HAMSTER OVARY CELLS.

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Mutat Res; 101(1):77-86 1982

Induction of sister-chromatid exchanges (SCE), chromosomal aberrations, and antiproliferative activity of DHAQ (a dihydroxy bis(aminoalkylamino)-substituted anthraquinone) and several related analogues were investigated in Chinese hamster ovary cells and the results compared with those of doxorubicin (DOX). Marked genotoxic effects were observed with DHAQ, DOX, and two analogues of DHAQ (compounds IIIc and IV), with the most potent effect observed with DHAQ. At 50 nanoM, DHAQ completely inhibited cells from entering second metaphase by the end of the 48-hr culture period; comparable effects were observed with 1,000 nanoM of the other compounds. At 1 nanoM, the frequency of SCE was similar between the agents, although DHAQ induced the most dramatic chromosomal aberrations. DHAQ induced a more potent genotoxic effect on the induction of chromosomal aberrations than on SCE induction. Compound IIIc enhanced SCE induction. DOX showed a linear dose response in its ability to induce chromosomal aberrations at concentrations of 10 and 200 nanoM; the SCE effect were not as obvious. Compounds IIIa, IIIb, and V significantly induced SCE; chromosomal aberrations were generally observed at lower concentrations than SCE. Antiproliferative effects of these agents were correlated with their genotoxic effects, with DHAQ having the most antiproliferative effect followed by DOX, compound IIIc, and compound IV; compound IIIb exhibited a significant effect only at 1,000 nanoM, while IIIa and V showed no antiproliferative effects. Genotoxic effects were always observe d at lower concentrations than antiproliferative effects. (24 Refs)

77. INDUCTION OF SISTER-CHROMATID EXCHANGES, CELL-CYCLE DELAY AND CHROMOSOMAL ABERRATIONS BY HUMAN URINE CONCENTRATES.

Beek B, Aranda I, Thomson E
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Mutat Res; 92(1/2):333-360 1982

Human urine concentrates (HUC) prepared using XAD-2 resin induced sister chromatid exchanges, chromosomal damage, and cell cycle delays in cultured Chinese hamster ovary cells, without the use of metabolic activation. The mutagenic activities of HUC from smokers, nonsmokers, and patients with alcoholic cirrhosis of the liver were about the same. Experiments with variant HUC preparative procedures showed that rapid saturation of the resin by nonpolar compounds from human urine may result in underestimation of the amount of mutagenic substances in a given HUC sample. (26 Refs)

78. DOUBLE-BLIND STUDY ON THE EFFECT OF CIGARETTE SMOKING ON THE CHROMOSOMES OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES IN VIVO.

Obe G, Vogt HJ, Madle S, Fahning A, Heller WD
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Mutat Res; 92(1/2):309-319 1982

The frequencies (expressed per 1,000 metaphases) of chromosomal aberrations (CAs) in peripheral blood lymphocytes (PBL) were studied in 170 smokers and 124 nonsmokers (all men) in a double-blind study. As compared to the nonsmokers, the smokers showed significantly higher mean frequencies of all CAs combined (2.01 vs 0.99), rings plus minutes (0.71 vs 0.24), chromatid translocations plus dicentrics (CT-D: 1.30 vs 0.67), and sister chromatid exchanges (SCEs: 5.78 vs 4.79). When subjects with histories of high alcohol consumption, several virus infections (including mumps), chronic drug treatment, and unusually high x-ray exposure were eliminated from the calculations, the CT-D frequencies in the PBL of smokers and nonsomokers (1.84 vs 0.83) were not significantly different, but the PBL of smokers continued to show a higher frequency of these CAs. The mean frequencies of second metaphases in 48-hr PBL cultures were significantly higher in the nonsmokers than the smokers (2.58 vs 1.74), indicating a depressive effect of smoking on phytohemagglutinin-induced lymphocyte stimulation. The mean frequencies of micronuclei in 3-day PBL cultures were the same in the smokers and nonsmokers (3.12 vs 2.97). It is concluded that structural CAs are better indicators of the cytogenetic effects of low-level chronic mutagen exposure in man than SCEs. (58 Refs)

79. IN VIVO AND IN VITRO EFFECTS OF CIGARETTE SMOKE ON CHROMOSOMAL DAMAGE AND SISTER-CHROMATID EXCHANGE IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES.

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Mutat Res; 92(1/2):321-332 1982

The frequencies of chromosomal aberrations in phytohemagglutinin-stimulated peripheral blood lymphocytes (PBL) were studied in 49 women and 47 men (20-75 yr old); 55 were smokers (mostly in the light-to-moderate range, 1-10 cigarettes/day) and 41 were nonsmokers. The mean frequencies of all chromosomal aberrations combined were significantly higher in the smokers than in the nonsmokers (3.20 vs 2.22%). These differences were greatest for the frequencies of interchanges (0.22 vs 0.02%), gaps (0.56% vs 0.24%), fragments (0.67 vs 0.34%), dicentrics (0.42 vs 0.14%), and unambiguous exchange-type aberrations (0.64 vs 0.17%). A comparison of PBL cultures from a small group of subjects (3 nonsmokers, 3 heavy smokers) showed a 50% higher baseline frequency of sister chromatid exchanges (SCEs) in the smokers (means, 11.6 vs 7.6 SCEs/cell). Exposure to cigarette smoke condensate (CSC: 0.1-1.5 mg/10 ml) caused dose-dependent increases in SCE frequencies in the PBL of both smokers and nonsmokers. The dose-response curves were parallel, suggesting that the apparently greater effects of CSC in causing SCEs in the PBL of smokers simply reflected the higher basal SCE frequencies in this group, although the smokers' PBL showed somewhat more unscheduled DNA synthesis in response to CSC than the nonsmokers' PBL. Mitomycin C (10(-8)-10(-7) M) and ethyl methanesulfonate (10(-4)-10(-3) M) caused dose-dependent increases in the SCE frequencies in PBL from both smokers and nonsmokers. The parallel dose-response curves noted with both agents in both types of PBL suggested that the results reflected the basal differences in SCE frequencies between the groups, as opposed to a greater intrinsic sensitivity to mutagens in the PBL of smokers. (19 Refs)

80. COMPARISON OF THE GENOTOXIC ACTIVITIES OF EXTRACTS FROM AMBIENT AND FOREST FIRE POLLUTED AIR.

Viau CJ, Lockard JM, Enoch HG, Sabharwal PS
Graduate Center for Toxicology, Univ. Kentucky, 202 Medical Center Annex 5, Lexington, KY, 40536
Environ Mutagen; 4(1):37-43 1982

The genotoxicity of soluble, organic extracts of airborne organic particles was tested with use of the Salmonella reversion assay and the sister chromatid exchange (SCE) assay in cultured human lymphocytes. Airborne particles were collected in high volume air samplers in a non-industrial urban area under normal conditions (ambient) and during a period when dense smoke from a forest fire was carried by the wind into the area of the collectors. Salmonella strains TA98 and TA100 were used with and without Aroclor-induced rat liver S9 homogenate. While each sample caused increases in revertants in the Ames assay and increased incidence of SCE/cell, on the basis of the volume of air sampled, smoke-filled air induced 12-14x more bacterial reversions in TA100 and 16-38x more in TA98 than ambient (non-smoky) air. On a volume basis, 'smoky' air induced 43x more SCE in human lymphocytes than did ambient air. On the basis of extract weight, the 'smoky' air extract induced more SCE in human lymphocytes, but fewer bacterial revertants in the absence of S9 than the extract of 'nonsmoky' airborne particles. (17 Refs)

81. CYTOGENETIC ACTIVITIES OF 3 SULPHONAMIDES.

Badr A
Botany Dept., Faculty Science, Tanta Univ., Tanta, Egypt
Mutat Res; 104(1-3):95-100 1982

Cytogenetic effects of three sulfonamides were tested in Allium cepa (cv Giza). Bulbs with growing root tips were exposed to sulfadiazine (2-p-aminobenzene sulfonamide pyrimidine), sulfadimidine (2-p-aminobenzene sulfonamide 5-p-aminomethyl pyrimidine), or sulfaphenazole (5-p-aminobenzene sulfonamide-1-phenyl pyrazole) at concentrations of 0.02, 0.2, 1.0, or 2.0 mg/ml for 4, 24, or 48 hr. Cytological effects were studied by means of the Feulgen squash technique. Compared with controls, mitotic indices (MI) were increased by all three test compounds after 4-hr exposures and reduced after 24-and 48-hr exposures. Reduction in MI were concentration-dependent. Increasing exposure time from 24 to 48 hr produced only slight additional reduction in MI. MI were reduced to less than 50% of control values by concentrations of 1 or 2 mg/ml. All three test compounds produced high frequencies of mitotic and chromosomal abnormalities (C-metaphases, multipolar mitoses, polyploidy, chromosome lagging, stickiness, bridges, and breakage) after 4-hr exposures. The frequency of abnormalities was decreased after 24-hr exposures and increased relative to 24-hr exposures by 48-hr exposures. Wide variations were observed among roots undergoing the same treatment. Mitotic abnormalities were more common after 4-hr exposures, while chromosomal abnormalities were more common after 24-or 48-hr exposures. Results suggest possible mutagenic effects in humans. (18 Refs)

82. STUDIES ON THE MUTAGENIC POTENTIAL OF THE PESTICIDE CHLORDIMEFORME AND ITS PRINCIPAL METABOLITES IN THE MOUSE HERITABLE TRANSLOCATION ASSAY.

Lang R, Adler ID
Res. Lab., Schering, Berlin/Bergkamen, W. Germany
Mutat Res; 92(1/2):243-248 1982

Random-bred NMRI/SPF male mice were treated for 7 wk (by gavage) with max tolerated doses of chlordimeforme (CDMF: 120 mg/kg/day) or one of its principal metabolites, N-formyl-4-chloro-o-toluidine (100 mg/kg/day) and 4-chloro-o-toluidine (200 mg/kg/day), then mated with untreated females. The treated mice and male F1 offspring were screened for fertility. Animals showing reduced fertility or sterility were examined cytogenetically, by scoring meiotic chromosomes for translocation multivalents or assessing mitotic cells for marker chromosomes. CDMF and both of its principal metabolites at toxic doses did not induce translocation heterozygosity. The positive control agent, triethylene melamine (0.05 mg/kg/day), gave the expected mutagenic response. (7 Refs)

83. EXPRESSION OF GENETIC DAMAGE INDUCED BY ALKYLATING AGENTS IN GERM CELLS OF FEMALE MICE.

Becker K, Schoneich J
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Mutat Res; 92(1/2):447-464 1982

The effects of trenimon (TR: 0.25 or 1 mg/kg, ip) and cyclophosphamide (CP: 150 mg/kg, ip) on germ cells were studied in female random-bred NMRI mice (10-13 wk old). Pre-ovulatory treatment with CP or the higher dose of TR caused an increase (significant with TR, slight with CP) in frequency of meiotic non-disjunction in the unfertilized oocytes but did not cause structural aberrations in second-metaphase oocytes. In mice treated with CP or the lower dose of TR before ovulation and mated with random-bred NMRI males up to 0.5 day after treatment, TR showed a strong clastogenic effect on the first-cleavage embryos (first-cleavage metaphase). Numerical and structural chromosome aberrations were observed in 63.39% of the embryos; most of the aberrations were structural aberrations of the chromatid types. The embryonic mortality rate was 55.17%, as measured in the dominant lethal assay. Similar treatment with CP enhanced the occurrence of dominant lethal effects to 58.94%. When the alkylating agents were given at longer times before mating (up to 23.5 days), their clastogenic and mutagenic effects declined with time. The results observed with TR support the conclusion that an intervening round of DNA replication is required for TR-induced DNA damage to be transformed into a structural aberration. (55 Refs)

84. A SEARCH FOR SOME COMMON CHARACTERISTICS OF THE EFFECTS OF CHEMICAL MUTAGENS IN DROSOPHILA.

Vogel EW, Blijleven WG, Kortselius MJ, Zijlstra JA
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Mutat Res; 92(1/2):69-87 1982

An analysis of shared general features was used to compare the actions of mutagens in Drosophila. Germ cell metabolism is the most significant factor determining the effects of promutagens in various cell stages. Only autosomal recessive lethal mutations can be used to compare stages sensitivity to a given mutation. Only a few mutagens have been tested in both sexes of Drosophila, including mitomycin C, bleomycin (BLM), and diethylstilbestrol. Females are much more sensitive than males to the mutagenic action of BLM, which causes recessive lethals and X-chromosomal aneuploidy in oocytes. The mutagenicities of some (not all) alkylating agents can be greatly modified by introducing repair-deficient mutants into the test system, but each new strain must be validated before it is tested with a wide variety of mutagens. The molecular mechanisms of the interactions of some methylating and ethylating agents with DNA are related to their genetic effects in germ cells. The relative proportions of chromosome aberrations to mutations and the ability of an agent to induce delayed mutations can be used to provide more information on the basic mechanisms of chemical mutagenesis. For at least some mutagens, a positive correlation has been discovered between the induction of chromosome aberrations in germ cells and the induction of an increased proportion of mosaic twin spots (relative to mosaic single spots) in somatic tissues. (68 Refs)

85. THE MUTAGENIC EFFECTS OF DIEPOXYBUTANE IN WILD-TYPE AND MUTAGEN-SENSITIVE MUTANTS OF DROSOPHILA MELANOGASTER.

Olsen OA, Green MM
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Mutat Res; 92(1/2):107-115 1982

The effects of 1,2,3,4-diepoxybutane (DEB) on two X-chromosome loci (w and y) of Drosophila were studied. At least one-third of the DEB-induced mutations were chromosome deletions. The nature of the DEB-induced complementary mutants was not clear. Some of the mutants were mosaics, expressed somatically but not transmitted in the germ line. Somatic sensitivity to DEB was demonstrated by 9/11 methyl methanesulfonate (MMS)-sensitive mutants. The MMS-sensitive and DEB-insensitive mutants were also somatically insensitive to nitrogen mustard and UV (one was also insensitive to x-rays), suggesting that these mutants (mus103 and mus105) may not be involved in DNA replication or repair. In direct genetic experiments, females homozygous for at least 2/6 and probably 5/6 MMS-sensitive mutants showed an impaired capacity to repair DEB-induced damage in spermatozoa. Females homozygous for MMS-sensitive mutant mus201 showed an unimpaired capacity to repair DEB-induced genetic damage. (15 Refs)

GENERAL REVIEWS

86. CURRENT STATUS OF CYTOGENETIC STUDIES IN ANIMAL TUMORS WITH SPECIAL REFERENCE TO NONRANDOM CHROMOSOME CHANGES.

Sasaki M
Chromosome Res. Unit, Hokkaido Univ., Faculty Science, Sapporo 060, Japan
Cancer Genet Cytogenet; 5(2):153-172 1982

The current status of animal tumor cytogenetics is reviewed with particular attention given to nonrandom karyotypic rearrangements and their implications in animal neoplasia. Tumors of the mouse discussed include thymic lymphoma, plasmacytoma, myeloid leukemia, hematologic, and nonhematologic tumors. Tumors of the rat discussed include leukemias, sarcomas, and transplanted tumors or cell lines studied by banding. Chromosome control of tumors in cultured hamster cells (Syrian and Chinese) is reviewed. (158 Refs)

87. A REVIEW OF THE MUTAGENICITY OF CHROMIUM.

Hatherill JR
Toxicology, Sch. Public Health, Univ. Michigan, Ann Arbor, MI, 48109
Drug Chem Toxicol; 4(3):185-195 1981

Prokaryotes testings for Cr(VI), gave the following results: (a) positive (frame-shift and base-pair) in Salmonella typhimurium strains TA1537, TA98, and TA100, while Cr(III) was negative at 100x as much; (b) Cr(VI) was positive (rec-effects) in Bacillus subtilis, while Cr(III) was negative; (c) Cr(VI) was positive (prototrophic revertants) in tryptophan auxotrophic strains of Escherichia coli and in E coli Hs30R. Eukaryotes testings gave for Cr(VI) positive (forward) results in Schizosaccharomyces pombe. In vitro Cr(VI) was: (a) positive (chromosomal variance) in Syrian hamster embryonic cells, while Cr(II) and (III) were negative at 7x as much; (b) Cr(VI) was positive (karyotypic damage) in mouse fetal cells, while Cr(III) was also positive; (c) Cr(VI) was positive (transformation) in BHK-21 fibroblast-like cells; (d) positive (chromosomal aberrations, CSA) in actively dividing human embryonal fibroblast and lymphocyte cells; (e) positive (CSA) in Chinese hamster ovary and embryonic cells; (f) positive (CSA) in human leukocytes, while Cr(III) was negative in heteroploidy except for expression of gap types of chromosomal variance; (g) Cr(VI) was positive (sister chromatid exchanges) in human fibroblasts and Chinese hamster ovary cells. In vivo Cr(VI) was positive (CSA) in unspecified mammals, and murine bone marrow showed nuclear fragments or micronuclei formation. (56 Refs)

OTHER RELATED STUDIES

88. MOLECULAR MECHANISM OF ADAPTATION OF CELLS TO LOW LEVELS OF CARCINOGENIC AGENTS.

Villani G
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Pathol Biol (Paris); 30(2):117-123 1982

Adaptation of Escherichia coli, rat liver cells and human fibroblasts to the cytotoxic and mutagenic effects of alkylating agents such as N-methyl-N'-nitro-N-nitrosoguanidine (MMNG), dimethylnitrosamine (DMN), and N-methylnitrosourea (MNUA) are reviewed. Through exposure to low doses of alkylating agents an increased numbers of cells are able to survive the challenge of high doses; fewer mutations are observed among survivors. Adaptation in E coli, a process involving DNA repair, is inducible and non-specific, consisting of two dissociable phenomenon (increased survival, decreased mutagenesis) controlled by gene polA, and is independent of other repair systems. Studies of adaptation to MNNG in E coli have shown that following adaptation, the methyl group is transferred from the O-6 position of guanine to an acceptor protein which is rapidly inactivated. After exposure to a challenge dose of DMN, fewer DNA O-6 methylguanine lesions were found in livers of rats preexposed to low doses of DMN for 4-6 wk as compared with untreated controls; the same number of N-7 methylguanine and N-3 methyladenine lesions were found in bot h groups. Pretreatment of cultured human fibroblasts with low doses of MNNG or MNNU increased their resistance to challenge; fewer sister chromatid exchanges were observed following the challenge. (41 Refs) (In FRE)

89. A METHOD FOR THE MEASUREMENT OF VARIABILITY IN CELL LIFETIMES.

Cowan R, Culpin D

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Math Biosci; 54(3/4):249-263 1981

The numbers of S-phases encountered by a cell during a known period of time were studied in chick embryo retinal cells continuously labeled with 5-bromo-2'-deoxyuridine (BUdR) and selectively stained. The BUdR-labeled cells were examined during metaphase or late prophase. In cells which had passed through 0-1 S-phases after BUrD exposure, both members of a given chromatid pair were darkly stained. The proportions of stained chromosomes declined after each successive cell division. This BUdR labeling method is a considerable refinement on the fraction-labeled mitosis technique, which determines only whether or not a cell has encountered an S-phase. (14 Refs)

90. COMPARISON OF CHROMOSOMAL STRUCTURES ISOLATED UNDER DIFFERENT CONDITIONS.

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Exp Cell Res; 138(1):221-229 1982

The biochemical nature of chicken chromosomes isolated using acidic solution (ie 50% acetic acid) and using a near neutral solution containing spermine, spermidine, EDTA and EGTA [9], were compared. In both cases, no swelling of the chromosomes was observed. Chromosomes isolated under near neutral conditions contain nucleosome structure, whereas in those isolated under acidic conditions the nucleosome structure is destroyed. This was determined by micrococcal nuclease digestion of the isolated chromosomes followed by gel electrophoresis of the chromosomal DNA. In addition, acidic treatment of the chromosomes resulted in irreversible changes in protein-DNA interactions in chromosomes, as judged by the sedimentation behaviors of the isolated chromosomes in a sucrose gradient containing 2 M NaCl, and by the accessibility of the DNA to restriction endonuclease digestion. The chicken ovalbumin gene in the chromosomes isolated using acidic solutions was highly accessible to digestion by restriction endonucleases, whereas most of the restriction enzyme cleavage sites were protected in the chromosomes isolated under near neutral conditions. These results suggest that acidic treatments of chromosomes, the method used most often for cytogenetic preparations, causes extensive damage to the biochemical nature of chromosome structure; and the solution utilized by Blumenthal et al [9] is a better solution for chromosome isolation. (Author abstract) (22 Refs)

91. MODIFICATIONS OF CHROMATIN STRUCTURE IN CONTROL OF GENE EXPRESSION.

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Med Hypotheses; 8(2):113-133 1982

The mechanisms controling gene expression and cellular differentiation in higher eukaryotic organisms are an active area of research in molecular biology. This article reviews what is known about chromatin structure and its regulations, and the following aspects are included the basic building block - the nucleosome,; the histone and nonhistone proteins which maintain chromosome structure and control transcription, the replication and transcription enzymes, repetitive sequences in DNA, DNA introns, and chromosomal RNA. A number of chromatin modifications such as DNA methylation and phosphorylation-dephosphorylation or acetylation-deacetylation of chromosomal proteins, and apparently involved in the control of gene expression are discussed. Tumor viruses and carcinogens may cause changes in chromatin structure resulting in a circumvention of normal cell cycle controls of proliferation. (68 Refs)

92. LONG-TERM EFFECTS OF AZATHIOPRINE IN RHEUMATOID ARTHRITIS.

Urowitz MB, Smythe HA, Able T, Norman CS, Travis C
Rheumatic Disease Unit, Wellesley Hosp., 160 Wellesley St. E., Toronto, Ontario, M4Y 1J3, Canada
Ann Rheum Dis; 41(Suppl1):18-22 1982

Potential early signs of malignancy were assessed in 36 patients (8 men, 28 women; mean age 57.8 yr) receiving azathioprine (APR: mean, 1.08 mg/kg/day x 38.5 mo) for rheumatoid arthritis and 49 controls (13 men, 36 women; mean age 51.4 yr) not receiving APR. The mean duration of arthritis was somewhat longer in the APR group (15.3 vs 11.9 yr). The groups were comparable in their symptomatic status, chest x-rays, and most laboratory test results. As compared to the controls, the APR groups showed significantly lower WBC counts, a higher frequency of megaloblastic features in the bone marrow, lower serum folate levels, and a higher frequency of chromosomal aberrations in the bone marrow. Malignancies had occurred in first-degree relatives of 15/36 APR-treated patients and 6/49 controls. The APR and control groups showed comparable frequencies of inflammatory or fibrotic pulmonary abnormalities (15/36 vs 9/49), benign breast masses (1/28 vs 3/36 women), and abnormal urine cytology (4/36 vs 1/49) with no evidence of cancer on follow-up. Neoplasms were observed in 7/36 APR patients (3/7 were malignant or potentially malignant tumors) and 5/49 controls (1/5 was a malignant tumor); the difference in incidence rates were not significant. The only non-Hodgkin's lymphoma observed in the group was in a control patient. In the APR group, the tumors developed after a mean of 1.6 yr of APR therapy. Three APR-treated patients with cancer had positive family histories of cancer; none of the controls with tumors had family histories of cancer. Elevated titers of alpha-fetoprotein or carcinoembryonic antigen were observed in some of the APR group (1/36 and 7/25 patients tested, respectively; none of these patients had a detectable cancer) and none of the controls. Further studies in larger groups of APR-treated patients and longer treatment periods are recommended. (53 Refs)

☆ U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/123

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SERIES CB12 No. 82/09

SEPTEMBER, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20.3173/2:

CLINICAL STUDIES OF CHROMOSOMES IN HUMAN CANCER

1. REARRANGEMENT OF CHROMOSOME NO. 3 IN A CASE OF PRELEUKEMIA WITH THROMBOCYTOSIS.

Norrby A, Ridell B, Swolin B, Westin J
(c/o Westin) Dept. Medicine, Ostra Hosp., S-416 85 Goteborg, Sweden
Cancer Genet Cytogenet; 5(3):257-263 1982

The clinical and cytogenetic findings of a patient with the preleukemic syndrome and a structural rearrangement involving both chromosomes No 3 are described. The karyotypic abnormality consisted of an insertion of a part of the long arm of one chromosome No 3 into the other, ie, ins(3;3)(q27;q21q27). A prominent feature of the bone marrow was a marked megakaryocytic hyperplasia. The platelet count temporarily exceeded 1,000 x 10(9)/liter. The findings of the present case, together with similar observations by others, suggest that the long arm of chromosome No 3 may contain a region involved in the regulation of megakaryopoiesis. (Author abstract) (15 Refs)

2. A PHOTOMETRIC STUDY OF THE STANDARD PHILADELPHIA (PH(1)) TRANSLOCATION OF CHRONIC MYELOID LEUKEMIA (CML).

Wayne AW, Sharp JC
Dept. Haematology, King's Coll. Hosp., Denmark Hill, London SE5 8RX, England
Cancer Genet Cytogenet; 5(3):253-256 1982

A newly developed form of high resolution microscope photometry has been employed in a study of the relationships between the chromosomes involved in the standard Philadelphia (Ph(1)) translocation of chronic myeloid leukemia (CML). The intention of the investigation was to provide quantitative data on the relative amount of material exchanged between the No 9 and No 22 chromosomes. A marked consistency in the amount of material lost from the Ph1 was observed, and the balanced nature of the standard Ph1 translocation was confirmed. The data are also in accordance with the concept of a reciprocal exchange between the No 9 and No 22 chromosomes. (Author abstract) (9 Refs)

DNA CONTENT AND PLOIDY CHANGES ASSOCIATED WITH CANCER

3. CYTOMETRIC EVIDENCE OF CYTOGENETIC AND PROLIFERATIVE HETEROGENEITY OF HUMAN SOLID TUMORS.

Nervi C, Badaracco G, Maisto A, Mauro F, Tirindelli-Danesi D, Starace G
Istituto Medico e di Ricerca Scientifica, 00191 Rome, Italy
Cytometry; 2(5):303-308 1982

Eleven cases of non-small cell carcinoma of the lung (primary or metastasis of different histological type) and 3 cases of non-neoplastic lung disease were studied by flow cytometry. The modal DNA content expressed as DNA index is reported. Except in one case all neoplastic lesions were characterized by the concomitant presence of a diploid peak with a modal DNA content higher than diploid. Aneuploidy was scattered apparently at random, with DNA index in the range 1.20-3.50. The three non-neoplastic cases showed normal diploid DNA content. In 3/11 neoplastic cases multiple clones of different DNA index were identified in more than one sample from the same tumor. The relative proportion of cells in the diploid and aneuploid peaks varied between tumors and in samples from different areas of the same tumor. Due to overlapping of normal and neoplastic DNA distributions or to the presence of overlapping multiple DNA distributions, the evaluation of cell fractions in the cycle phases was performed in only 3/11 neoplastic cases. The main problem was in obtaining reliable estimations in specimens characterized by a DNA distribution of complex structure. Flow cytometry has been applied routinely to analyze mainly head and neck squamous cell carcinoma and breast carcinoma. (11 Refs)

4. DNA CONTENT OF CELLS WITH GENERALIZED CHROMOSOME SHATTERING INDUCED BY ULTRAVIOLET LIGHT PLUS CAFFEINE.

Cremer C, Gray JW
Biomedical Sciences Div., Lawrence Livermore Natl. Lab., Univ. California, Livermore, CA, 94550
Mutat Res; 94(1):133-142 1982

The results of flow cytometric analyses of DNA content of UV and caffeine-treated Chinese hamster ovary (CHO) cells are reported. CHO cells growing asynchronously were exposed to 5.0 Joules/square meter UV (254 nanometer) and then incubated with or without 2 milliM caffeine. Very few generalized chromosome shattering (GCS)-cells were observed in control cultures or in cultures treated with UV or caffeine alone. However, the GCSm (number of cells with GCS-like appearance/number of cells with condensed, chromosome-like chromatin x 100) and GCSt (%GCSm x mitotic index) increased sharply to 86 and 10, respectively, after treatment with UV plus caffeine. Fluorescence distributions for control, UV-treated and caffeine-treated cells were very similar. Peak B in fluorescence distributions of UV- and/or caffeine-treated cells corresponded to a normal G2M content. All GCS-like cells were found to have the G2M DNA content. These results suggest a subtle process resulting in failure of normal chromosome condensation after most or all of the DNA has been replicated in GCS-like cells. (29 Refs)

5. DISCRIMINATION OF G1, S, AND G2 CELLS USING HIGH-RESOLUTION TV-SCANNING AND MULTIVARIATE ANALYSIS METHODS.

Abmayr W, Giaretti W, Gais P, Dormer P
Institut fur Strahlenschutz, Gesellschaft fur Strahlen-und Umweltforschung mbH Munchen, Ingoldstadter Landstrasse 1, 8042 Neuherberg, W. Germany
Cytometry; 2(5):316-326 1982

Exponentially growing mouse L-fibroblasts were investigated to determine whether densitometric, geometric, textural, and chromatin features could be used to discriminate cells in different phases of the cell cycle. Using autoradiography and DNA content, the cellular data set was divided into labeled and unlabeled cells, and the latter subdivided into G1 and G2 cells. Of 781 cells analyzed, 176 were in G1, 470 in S, and 135 in G2 phase. Visual distinction into high-label and low-label of individual cells did not provide a reliable subclassification. Classification was performed using the nuclear DNA content alone. The classification matrix showed the difficulty of correctly discriminating between G2 and late S cells. A total of 69.4% of the cells were classified correctly, but only 51.1% of the S cells were correctly identified with this method. Results of the classification with six features and the scatter plot of the first vs the second canonical variable of these six features are presented. Results improved to a 75.3% classification and the discrimination of S cells was raised to 60.0%. Using only textural and chromatin features for analysis, the classification was 79.4% and the S cell discrimination improved to 69.8%. The mean values of the discriminating operators for the 14 selected features clearly showed more overall discriminating power for the G1 vs S classification. (18 Refs)

CHROMOSOMAL FRAGILITY AND GENETIC FACTORS PREDISPOSING TO HUMAN CANCER

6. TWIN PREGNANCY WITH COMPLETE HYDATIDIFORM MOLE (46,XX) AND FETUS (46,XY): GENETIC ORIGIN PROVED BY ANALYSIS OF CHROMOSOME POLYMORPHISMS.

Fisher RA, Sheppard DM, Lawler SD
Inst. Cancer Res., Royal Marsden Hosp., London SW3 6JJ, England
Br Med J; 284(6324):1218-1220 1982

In a case of complete hydatidiform mole with fetus the genetic origins were defined by the use of chromosomal polymorphisms. The fetus had a normal 46,XY karyotype with evidence of the presence of both maternal and paternal chromosomes. The mole was 46,XX and of androgenetic origin. There was no evidence of a maternal contribution, and duplication of paternal chromosomes was shown. In such atypical molar pregnancies examining genetic polymorphisms yields much more information than do sex chromosome studies and karyotyping, particularly in confirming the diagnosis and defining the origin and etiology of the condition. (Author abstract) (26 Refs)

7. SCE AND UDS STUDIES IN A FAMILY WITH RETINOBLASTOMA: A CASE STUDY.

Fabricant JD, Au W, Fabricant RN, Morgan KS
Dept. Preventive Medicine and Community Health, Div. Genetic Toxicology, Univ. Texas medical Branch, Galveston, TX
Teratogenesis Carcinog Mutagen; 2(1):85-90 1982

Lymphocytes from a father and daughter with retinoblastoma were analyzed for spontaneous and mitomycin C (MMC)-induced sister chromatid exchanges (SCE) and unscheduled DNA synthesis (UDS) induced by MMC and M-methyl-N-nitro-N-nitrosoguanidine (MNNG), compared to results from two controls. Cells for the SCE studies were treated with 10(-8) and 10(-7) M MMC, and those for the UDS studies with 0.3-10 ug/ml MMC or 1-30 x ug/ml MNNG. SCE were identified after staining by the fluorescent-plus Giemsa technique, and UDS by incorporation of 3H-thymidine. Spontaneous and induced SCE frequencies were similar in retinoblastoma and control lymphocytes. UDS was the same for both groups after MMC treatment, but was not increased in the experimental group after MNNG treatment, as compared to an increase seen in the control group. Results indicate that lymphocytes from retinoblastoma patients respond normally to the cross-linking agent MMC, but are unable to repair DNA damage caused by the alkylating agent MNNG. (18 Refs)

8. RETINOBLASTOMA IN A BOY WITH A DE NOVO MUTATION OF A 13/18 TRANSLOCATION: THE ASSUMPTION THAT THE RETINOBLASTOMA LOCUS IS AT 13Q141, PARTICULARLY AT THE DISTAL PORTION OF IT.

Motegi T, Komatsu M, Nakazato Y, Ohuchi M, Minoda K
Dept. Pediatrics, Tokyo Univ. Branch Hosp., 3-28-6, Mejirodai, Bunkyo-ku, Tokyo 112, Japan
Hum Genet; 60(2):193-195 1982

Chromosomal banding studies in retinoblastoma patients indicated that the common deleted segment was 13q14. The case presented is interesting because of the simultaneous occurrence of sporadic retinoblastoma and a de novo mutation of a 13/18 translocation with respective breakpoints at 13q141 and 18q122. The study suggests that the gene locus for retinoblastoma is at 13q141. The high resolution sub-band technique using early mitotic cells may contribute to retinoblastoma gene mapping. (11 Refs)

9. GENETIC HETEROGENEITY IN ATAXIA-TELANGIECTASIA STUDIED BY CELL FUSION.

Jaspers NG, Bootsma D
Lab. Cell Biology and Genetics, Erasmus Univ. Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands
Proc Natl Acad Sci USA; 79(8,part1):2641-2644 1982

The effect of x-rays on the rate of semiconservative DNA replication was investigated by autoradiography in single cells obtained from normal individuals and from patients having ataxia-telangiectasia (AT). In the five AT cell strains studied, the rate of DNA synthesis was inhibited to a lesser extent than in two normal cell strains. By using this abnormal regulation of DNA replication in AT cells as a marker, an experimental procedure was developed that allowed genetic complementation analysis of AT. After Sendai virus-induced fusion of AT cells, the grains were counted over binucleate cells with both nuclei in S phase. In some cases, the inhibition of DNA synthesis caused by x-rays in the heterodikaryons was more pronounced than that in the parental homodikaryons and was comparable to that in normal binucleate cells, indicating complementation. By using this approach, the five AT cell strains that were investigated could be assigned to three complementation groups. The data suggest that extensive genetic heterogeneity exists in AT. (Author abstract) (15 Refs)

10. FREQUENCY OF UV-INDUCED NEOPLASTIC TRANSFORMATION OF DIPLOID HUMAN FIBROBLASTS IS HIGHER IN XERODERMA PIGMENTOSUM CELLS THAN IN NORMAL CELLS.

Maher VM, Rowan LA, Silinskas KC, Kateley SA, McCormick JJ
Carcinogenesis Lab., Michigan State Univ., Fee Hall, East Lansing, MI, 48824
Proc Natl Acad Sci USA; 79(8,part1):2613-2617 1982

If neoplastic transformation of diploid human cells results from carcinogen-induced mutations, cells deficient in excision repair of UV-induced DNA damage should be significantly more sensitive to transformation by UV light than normal cells. We tested this hypothesis by irradiating fibroblasts from a xeroderma pigmentosum patient (XP7BE, complementation group D) with low doses of UV light (254 nm) and cells from a normal person with much higher doses and comparing the frequency of transformation to anchorage independence. Both sets of cells exhibited a dose-dependent increase in transformation which corresponded to a dose-dependent decrease in survival.

At doses that caused equal cell killing, the frequency of anchorage-independent cells was approximately equal. Colonies of XP7BE and normal cells isolated from agar, propagated, and injected into x-irradiated athymic mice produced fibrosarcomas in 100% of the animals. Normal cells irradiated shortly before the onset of DNA synthesis exhibited a high frequency of anchorage-independent cells; cells irradiated in early G1 showed no increase over background. These results agree with those we observed for UV induction of 6-thio-guanine-resistant mutants in these cells and support the hypothesis that anchorage independence results from mutations induced by DNA replication on a damaged template. (Author abstract) (21 Refs)

11. WILMS' TUMOR WITH ANIRIDIA/IRIS DYSPLASIA AND APPARENTLY NORMAL CHROMOSOMES.

Riccardi VM, Hittner HM, Strong LC, Fernbach DJ, Lebo R, Ferrell RE

Res. Cytogenetics Lab., Baylor Coll. Medicine, 1200 Moursund Ave., Houston, TX, 77030

J Pediatr; 100(4):574-577 1982

Two patients with Wilms' tumor, iris dysplasia (complete aniridia in one and subtle iris defects in the other), normal karyotypes, and no gene loss demonstrable by enzyme marker and direct DNA analyses are presented. The findings indicate that aniridia and less severe iris defects define a risk for Wilms' tumor even in the absence of del (11p13), and that there is as yet no consistent biochemical genetic marker for the aniridia-Wilms tumor association. (Author abstract) (17 Refs)

CHROMOSOMES OF HUMAN CELL LINES AND TUMORS IN VITRO

12. PHENOTYPIC AND GENOTYPIC CHARACTERISTICS OF A CELL LINE FROM A SQUAMOUS CELL CARCINOMA OF HUMAN SKIN.

Boukamp P, Tilgen W, Dzarlieva RT, Breitkreutz D, Haag D, Riehl RK, Bohnert A, Fusenig NE

(c/o Fusenig) Deutsches Krebsforschungszentrum (DKFZ), 6900 Heidelberg, W. Germany

JNCI; 68(3):415-427 1982

A human cell line (SCL-1) from a poorly differentiating cutaneous squamous cell carcinoma (SCC) was studied through 20 passages during 2 yr. Cells maintained their original morphology with low degree of keratinization, as indicated by light and electron microscopy. The keratin peptide pattern resembled the type in SCC tumors, and the corresponding filaments were detected by immunofluorescence at all passage levels. Cells did not grow in soft agar but formed tumor-like nodules in an 'organotypic' culture assay (on lifted collagen gels) and grew invasively after transplantation to immunosuppressed inbred C3H mice. After injection into BALB/c nu/nu mice, tumors of SCC morphology were formed. The hypodiploid tumor stemline was maintained for about 10 passages, when a shift to hyperploidy started, as determined by chromosome and DNA flow microfluorometric analyses. Two stable marker chromosomes (in 100 and 70% of the metaphases, respectively), involving chromosomes 7 and 9, strongly indicated a monoclonal origin of this cell line. (Author abstract) (56 Refs)

CHROMOSOMES OF ANIMAL CELL LINES AND TUMORS

13. CO-EXPRESSION OF MOUSE AND RAT HEMOGLOBINS IN INTERSPECIFIC HYBRIDS OF MOUSE AND RAT ERYTHROLEUKEMIA CELLS.

Greiser-Wilke I, Steinheider G, Jentsch E, Arndt-Jovin D, Kluge N, Eibl HJ, Ostertag W

Max-Planck-Institut fur Molekulare Genetik, Ihnestrasse 63-73, D-1000 Berlin 33, W. Germany

Leuk Res; 6(1):9-15 1982

Hybrids from mouse and rat erythroleukemia cell lines were analyzed. Hybridization was done by a modified lysolecithin-lipid emulsion technique between Friend leukemia mouse cells and D5A1 rat erythroleukemia cells. The hybrids were selected in HAT (hypoxanthine, aminopterin, thymidine) medium. Two mo after culture chromosome analysis gave an almost tetraploid number, with no detectable chromosome loss and all markers present. Analysis of globin by carboxymethylcellulose chromatography after induction of erythroid differentiation by dimethylsulfoxide showed globin chains from both species. These findings demonstrate that both subsets of regulatory genetic material for inducible erythroid differentiation were compatible irrespective of the tumor character of the parental cell lines. (33 Refs)

14. NON-RANDOM CHROMOSOMAL CHANGES INVOLVING CHROMOSOMES 6 AND 7 IN SPONTANEOUS RAT IMMUNOCYTOMAS.

Wiener F, Babonits M, Spira J, Klein G, Bazin H

Departement Tumor Biology, Karolinska Institutet, S 104 01 Stockholm, Sweden

Int J Cancer; 29(4):431-437 1982

G-banding analysis of seven Ig-secreting spontaneous rat immunocytomas showed a consistent translocation of the distal part of the q-arm of chromosome 7 to the telomeric end of chromosome 6. The breakpoints were assigned to q3.3 on chromosome 7 and q3.2 on chromosome 6. Previously, we found a similar translocation pattern in mouse plasmacytomas induced by different agents. The distal part of the q-arm of chromosome 15 was translocated to the telomeric end of chromosome 12, known to carry Igh, the immunoglobulin heavy chain cluster. The banding homologies between the chromosomes involved in the translocations in the two species suggest that a similar mechanism is responsible for plasmacytomagenesis in both. We also predict that the rat Ig heavy chain gene cluster will be located to the terminal segment of chromosome 6. (Author abstract) (24 Refs)

15. GENERATION OF TUMOR CELLS WITH REDUCED DNA CONTENT AS A RESULT OF MACROPHAGE TUMORICIDAL ACTIVITY.

Connolly KM, Kaplan AM

(c/o Kaplan) Dept. Surgery and Microbiology, Medical Coll. Virginia, Richmond, VA, 23298

Cancer Res; 42(6):2198-2206 1982

Inoculation of pyran or Corynebacterium parvum ip in mice with Ehrlich ascites (EA) tumor cells induced a dramatic reduction in the EA tumor content of the peritoneal exudate. Cell cycle analysis of peritoneal exudate cell DNA content revealed that cells from untreated tumor-bearing mice possessed a DNA content approx 4C to 8C characteristic of aneuploid EA cells, while the pyran- or C parvum-treated animals had a larger complement of cells with a 2C DNA content and a loss of cells with an 8C DNA content. To determine what percentage of the 2C population was EA cells, the phenotype of the peritoneal exudate cell population was analyzed by indirect immunofluorescence with anti-host H-2 antisera. Since the EA cells lacked host H-2 markers, after accounting for the 2C H-2-positive host cells, we demonstrated that, in pyran- or C parvum-treated EA-bearing mice, 11 to 53% of the 2C population was EA cells possessing approx half their normal complement of DNA. Therefore, the tumoricidal activity of pyran- or C parvum-activated macrophages might be due in part to their ability to cause the formation of tumor cells with a reduced content of DNA. In other experiments in vivo, thioglycollate injection failed to elicit tumoricidal activity, as did pyran injection into mice previously irradiated or given injections of silica, suggesting that tumoricidal activity was mediated by macrophages. The proposed activated macrophage-mediated tumoricidal events demonstrated in vivo were substantiated by studies in vitro showing a direct relationship between the cytotoxic properties of C parvum-activated macrophages and their ability to induce tumor cells with a reduced DNA content, as well as a shift from G2-M to G1 in the remaining aneuploid tumor cells. We suggest that induction of tumor cells with a reduced content of DNA is a possible mechanism or consequence of activated macrophage tumoricidal activity. (Author abstract) (52 Refs)

16. PROPERTIES OF T ANTIGEN-POSITIVE PHENOTYPIC REVERTANTS ISOLATED FROM SV40-TRANSFORMED RAT AND MOUSE CELLS.

Maruyama K, Furuta T, Ueda K, Oda K
(c/o Oda) Dept. Tumor Virus Res., Inst. Medical Science, Univ. Tokyo, Shirokanedai, Minato-ku, Tokyo 108, Japan
Microbiol Immunol; 26(1):31-40 1982

T antigen-positive revertants isolated from SV40-transformed rat and mouse cells, which integrate six and two genome equivalents of viral DNA per cell respectively, were tested for tumorigenicity in nude mice and the relationship between tumorigenicity and karyological and growth properties of the cells was investigated. Three phenotypic revertants, R14, R15, R16, were isolated from W-3Y-23 cells. In soft agar medium, W-3Y-23 cells formed large colonies, R16 cells formed slightly smaller colonies, and neither R14 nor R15 formed large colonies. Revertant R14 showed a marked increase in the number of chromosomes to a median value of 130 and no subtetraploid cells were observed in their population. R15 and R16 showed a subtetraploid distribution similar to the parent cell line. W-3Y-23 cells were strongly tumorigenic and all the mice that received either high or low dose developed tumors within a wk. No tumors developed within 11 wk when approx 10(7) 3Y1-B, R14, or R15 cells were injected. R16 cells induced tumors that developed very slowly and became visible 8 wk after inoculation. All the tumors developed at the site of injection. R14, R15, and R16 cell DNA as well as W-3Y-23 DNA were cleaved with EcoRI which cuts the SV40 DNA once, and the DNA fragments containing the viral DNA sequence were analyzed. W-3Y-23 DNA generated seven distinct bands which were identical to those previously detected. Similar patterns were observed with all the revertant DNA; however the second and fourth bands from top of the gel were absent in all revertant DNA. In addition, the smallest band was generated from R14 and R15 DNA. The results indicate that a part of the viral DNA sequence had been deleted in all the revertants, while they still retained at least one complete viral genome. (19 Refs)

GENE MAPPING STUDIES

17. HUMAN IMMUNOGLOBULIN HEAVY CHAIN GENES MAP TO A REGION OF TRANSLOCATIONS IN MALIGNANT B LYMPHOCYTES.

Kirsch IR, Morton CC, Nakahara K, Leder P
Lab. Molecular Genetics, Natl. Inst. Child Health and Human Development, Bethesda, MD, 20205
Science; 216(4543):301-303 1982

A human immunoglobulin heavy chain (gamma4) gene is mapped by chromosome hybridization in situ. This gene is located at band 14q32, a site commonly involved in a chromosomal translocation characteristic of malignant B cells. (Author abstract) (45 Refs)

18. CHROMOSOMAL LOCATION OF A HUMAN ALPHA INTERFERON GENE FAMILY.

Slate DL, D'Eustachio P, Pravtcheva D, Cunningham AC, Nagata S, Weissmann C, Ruddle FH
Cancer Metastasis Research Group, Pfizer Central Research, Groton, CT, 06340
J Exp Med; 155(4):1019-1024 1982

A series of human/rodent somatic cell hybrids were scored for the presence of DNA sequences hybridizing to an alpha-1 interferon DNA probe. Hybrids were generated by fusing Chinese hamster E36 cells with human BD melanoma cells, temperature-sensitive Chinese hamster ovary cells and human WBC, mouse A9 cells with GM17 human fibroblasts, or mouse A9 cells with GM589 human fibroblasts. Hybrids were karyotyped and tested for the presence of human marker isozymes. In human/Chinese hamster hybrid cells, sequences hybridizing to the human alpha1 interferon probe were clearly observed in cellular DNA when chromosome 9 was retained. In hybrids lacking chromosome 9, no human-specific bands were observed. Segregation of chromosome 9 below a frequency of 20-30% resulted in a failure to detect alpha1 interferon related sequences. With appropriate cell hybrids, it should be possible to map rodent alpha interferon-related DNA sequences. (25 Refs)

19. EXPRESSION OF HUMAN TRANSFERRIN RECEPTOR IS CONTROLLED BY A GENE ON CHROMOSOME 3: ASSIGNMENT USING SPECIES SPECIFICITY OF A MONOCLONAL ANTIBODY.

Goodfellow PN, Banting G, Sutherland R, Greaves M, Solomon E, Povey S
Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Somatic Cell Genet; 8(2):197-206 1982

The species specificity of the monoclonal antibody OKT-9 was exploited to map a gene controlling human transferrin receptor expression using human-mouse somatic cell hybrids. Of 14 independent somatic cell hybrids tested, 6 were positive for OKT-9 and 8 were negative. The only human chromosomes present in all positive hybrids were chromosome 3 and the X chromosome. Since the X chromosome was present in 5/8 of the negative hybrids and human chromosome 3 was absent from all of these, it appeared that human chromosome 3 was necessary for expression of the OKT-9 antigen. Chromosome 3 linkage was confirmed in two independent sets of subclones. Immunoprecipitation analysis demonstrated that OKT-9 precipitated a 180,000 dalton mol wt-molecule from human cells, which, under reducing conditions, yielded a band of approx 90,000 daltons. A molecule with similar properties was precipitated from a human chromosome 3-containing hybrid. No specific immunoprecipitates with OKT-9 were obtained from a human chromosome-3-negative subclone and a mouse parental cell line. Thus, the gene controlling human transferrin receptor expression is on human chromosome 3. The gene for the human transferrin receptor and that controlling transferrin expression may be linked in humans. (42 Refs)

20. EXCLUSION OF LINKAGE BETWEEN LOCI FOR MULTIPLE ENDOCRINE NEOPLASIA TYPE-2 (MEN-2) AND HLA.

Simpson NE, Falk J

Dept. Pediatrics, Queen's Univ., 20 Barrie St., Kingston, Ontario, Canada

Hum Genet; 60(2):157 1982

Data on four nuclear families for which the phases of multiple endocrine neoplasia type-2 (MEN-2) and the HLA haplotypes were known and one family for which the phase of disease was not known exclude a previous hypothesis that there was linkage between the disease locus and the loci in the HLA complex. A recombination fraction of 0.5 was determined for the four families with known phase, thus excluding linkage. These data are consistent with the suggestion that MEN-2 is associated with a small deletion on chromosome 20, while HLA loci are on chromosome 6. (7 Refs)

MOLECULAR CYTOGENETICS

21. GENE TRANSFER INTO THE MOUSE GERM-LINE.

Costantini F, Lacy E

Dept. Zoology, Univ. Oxford, Oxford OX1 3PS, England

J Cell Physiol; Suppl1:219-226 1982

Introduction of a cloned rabbit beta-globin gene into mice by microinjection of fertilized eggs is described. The DNA used consisted of a 19 kilobase (kb) rabbit DNA fragment containing the adult beta-globin gene and a beta-like pseudogene, which is cloned in the bacteriophage lambda vector CH4A. Fifty-one mice were obtained from eggs that had been injected with a mixture of linear monomeric lambdaRbetaG2 DNA (80-90%) and concatemeric lambdaRbetaG2 DNA (10-20%). Nine of 24 screened mice contained copies of lambdaRbetaG2 in liver DNA. Of the nine mouse DNA samples, five showed a hybridization pattern characteristic of lambdaRbetaG2 DNA (lanes and l), while the other four showed no hybridization to the rabbit beta-globin probe. Four male and two female mice tested transmited the rabbit DNA fragments to a fraction of their offspring. The transmission of lambdaRbetaG2 sequences by one mouse to two out of six of its progeny was demonstrated. When the mouse DNA were digested with EcoRI (which cleaves the 19 kb and 10.7 kb lambda vector arms from the rabbit DNA insert) and probed with 32P-labeled lambdaRbetaG2, a 30 kb band was seen in every case instead of the 19 kb and 10.7 kb bands. Most of the mouse DNA showed a few fainter new EcoRI bands that hybridize with the lambdaRbetaG2 probe. These bands were of different mol wt in each of the original positive mice and were inherited by the progeny. Definite evidence for chromosomal integration was obtained for one parent mouse by in situ hybridization to metaphase chromosome spreads prepared from peripheral blood. (27 Refs)

22. DNA TRANSFER OF FOCUS- AND TUMOR-FORMING ABILITY INTO NONTUMORIGENIC CHEF CELLS.

Smith BL, Anisowicz A, Chodosh LA, Sager R

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Proc Natl Acad Sci USA; 79(6,part1):1964-1968 1982

CHEF/18 fibroblastic cells derived from a Chinese hamster embryo are diploid and nontumorigenic and require multiple steps of chemical treatment and selection to produce tumorigenic derivatives. In this report, CHEF/18 cells and a mutant capable of growing in medium with a low concentration of serum, LS1-1, were recipients in DNA transfer experiments using the calcium phosphate coprecipitation method. Focus formation with donor DNAs from tumor-derived CHEF cells and from human bladder carcinoma cell line EJ gave yield of 0.02-0.59 focus per ug of DNA per 10(6) recipients. IN one experiment in which CHEF/18 cells were transfected with EJ DNA, the presence of human DNA was detected in five of seven foci by using a cloned Alu sequence. Cells from one of these foci gave rise to tumors in nude mice, and the DNA produced secondary CHEF/18 transfectants. Because normal human cells as well as CHEF/18 cells require multiple stages to become tumorigenic, these findings suggest that EJ cells contain tumor-inducing DNA as the result of prior changes that occurred during the development of this carcinoma. (Author abstract) (39 Refs)

23. TRANSFORMATION WITH DNA FROM 5-AZACYTIDINE-REACTIVATED X CHROMOSOMES.

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Proc Natl Acad Sci USA; 79(7):2352-2354 1982

It has been shown that 5-azacytidine (5-Aza-Cyd) can reactivate genes on the inactive human X chromosome. It is assumed that the 5-Aza-Cyd acts by causing demethylation of the DNA at specific sites, but this cannot be demonstrated directly without a cloned probe. Instead, we have utilized the technique of DNA-mediated transformation to show that the 5-Aza-Cyd-induced reactivation occurs at the DNA level. DNAs from various mouse-human or hamster-human hybrid cell lines, deficient for mouse or hamster hypoxanthine phosphoribosyltransferase (HPRT; EC2.4.2.8), and varying in whether they contained either an active or inactive human X chromosome, were used in transformation of HPRT- cells. DNA from the active human X chromosome-containing cell lines yielded HPRT+ transformants, whereas DNA from the inactive X chromosome-containing cell lines did not. The inactive X chromosomal DNA was able to transform thymidine kinase-deficient mouse cells, indicating that the DNA solution was normal. These results confirm that inactivation of the X chromosome involves a DNA modification. Furthermore, DNAs from three cell lines with a 5-Aza-Cyd-reactivated X chromosome also transform HPRT- cells, demonstrating that the 5-Aza-Cyd has altered the DNA structure and supporting the idea that methylation plays a role in X chromosome inactivation. (Author abstract) (22 Refs)

24. REPAIR DNA SYNTHESIS IN HETEROKARYONS DURING REACTIVATION OF CHICK ERYTHROCYTES FUSED WITH HUMAN DIPLOID FIBROBLASTS OR HELA CELLS.

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Exp Cell Res; 138(2):469-474 1982

Suppression of unscheduled DNA synthesis (UDS) after exposure to ultraviolet (UV) light in the human nuclei results when diploid human fibroblasts are fused with chick erythrocytes. The suppression is positively correlated with the number of erythrocyte nuclei in the heterokaryons, with a maximal effect at 36 hr after fusion. Evidence is presented that this suppression is due to lowered levels of the enzymes involved in UDS as a result of inhibition of the RNA synthesis by chick components. No suppression of UDS is detected in the human nuclei of the HeLa-chick erythrocyte heterokaryons. In HeLa cells the rate of RNA synthesis is about 10x higher than the rate in the normal diploid fibroblasts, and the relatively small inhibitory influence of the chick components will therefore not lead to a limitation of the enzymes involved in UDS in the HeLa-chick erythrocyte heterokaryons. (Author abstract) (7 Refs)

25. SCINTILLOMETRIC DETERMINATION OF DNA REPAIR IN HUMAN CELL LINES: A CRITICAL APPRAISAL.

Bianchi V, Nuzzo F, Abbondandolo A, Bonatti S, Capelli E, Giorio R, Giulotto E, Mazzaccaro A, Stefanini M, Zaccaro L, Zantedeschi A, Levis AG
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Mutat Res; 93(2):447-463 1982

The ability of a UV- and x-irradiation and a variety of chemical agents to stimulate DNA repair synthesis in human heteroploid EUE cell cultures was tested by a simplified (3H)thymidine-incorporation scintillometric procedure, with the use of hydroxyurea (HU) to suppress DNA replicative synthesis. The percentage residual DNA synthesis, the absolute increase in DNA radioactivity, as the ratio treated/control, the relative increase in DNA radioactivity, which is an index of DNA repair stimulation, and unscheduled DNA synthesis as measured by autoradiography were determined. The agents used fell into four groups: inhibitors of DNA replication, with evident absolute and relative increases in radioactivity, inhibitors of replication with relative but not absolute increases in radioactivity, compounds not altering any observed parameter, and inhibitors of replication giving negative absolute and relative increases in DNA radioactivity. The procedure described is an improved approach to screening chemicals able to induce DNA repair in mammalian cell cultures, which avoids time-consuming autoradiographic analysis when the scintillometric parameters are definitely positive or negative. (45 Refs)

26. GENETIC AND BIOCHEMICAL CONSEQUENCES OF THYMIDYLATE STRESS.

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Can J Biochem; 60(3):172-194 1982

We have examined the genetic and biochemical consequences of thymidylate stress in haploid and diploid strains of the simple eukaryote Saccharomyces cerevisiae (Bakers' yeast). Previously we reported that inhibition of dTMP biosynthesis causes 'thymineless death' and is highly recombinagenic, but apparently not mutagenic, at the nuclear level; however, it is mutagenic for mitochondria. Concurrent provision of dTMP abolishes these effects. Conversely, excess dTMP is highly mutagenic for nuclear genes. It is likely that DNA strand breaks are responsible for the recombinagenic effects of thymidylate deprivation; such breaks could be produced by reiterative uracil incorporation and excision in DNA repair patches. In our experiments, thymidylate stress was produced both by starving dTMP auxotrophs for the required nucleotide and also by blocking de novo synthesis of thymidylate by various antimetabolites. We found that the antifolate methotrexate is a potent inducer of mitotic recombination (both gene conversion and mitotic crossing-over). This suggests that the gene amplification associated with methotrexate resistance in mammalian cells could arise, in part, by unequal sister-chromatid exchange induced by thymidylate stress. In addition, several sulfa drugs, which impede de novo folate biosynthesis, also have considerable recombinagenic activity. (Author abstract) (138 Refs)

27. CELLULAR SEQUENCES RELATED TO THREE NEW ONC GENES OF AVIAN SARCOMA VIRUS (FPS, YES, AND ROS) AND THEIR EXPRESSION IN NORMAL AND TRANSFORMED CELLS.

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J Virol; 42(1):143-152 1982

Two onc genes of avian sarcoma viruses unrelated to the src gene have recently been identified: fps of Fujinami sarcoma virus/PRCII/UR1 and yes of Y73/Esh sarcoma virus. In the first part of this study we demonstrated that UR2, the most recently isolated avian sarcoma virus, contains in its genome a unique sequence, ros, nonhomologous to src, fps, and yes sequences or to transforming genes of avian acute leukemia viruses. Using cDNAs specific to the inserts of avian sarcoma virus genomes, we examined the existence and the transcription of cellular nucleotide sequences related to the three new onc genes of avian sarcoma virus (fps, yes and ros) in various cells. The progenitor cellular sequences for these onc genes (c-onc) were present in uninfected chicken DNA in one or few copies per haploid genome. These c-onc sequences were detectable in cellular DNA of a wide variety of vertebrates, and the homology between viral and cellular onc was inversely related to the phylogenetic distance of animal species. The pattern of expression of these c-onc genes in different tissues of chickens was found to be unique to each gene. The expression of c-fps and c-ros genes was generally repressed in many tissues, but c-fps was expressed at higher levels in bone marrow (2.5 copies per cell) and lung (1.1 copies per cell), whereas c-ros was mainly transcribed in kidney (2.5 copies per cell). On the other hand, c-yes transcripts were easily detectable in all tissues analyzed and were found at high levels in kidney (26 copies per cell). These c-onc expressions were unaffected by infection with avian sarcoma viruses that contained other onc genes. In a few cultures of chicken and quail transformed cells derived from tumors induced by chemical carcinogens, we found that the levels of transcription of the four c-onc genes remained unaltered, compared with that in normal tissues. (Author abstract) (60 Refs)

28. REACTIVATION OF UV AND GAMMA-INACTIVATED HERPES VIRUS IN BHK CELLS.

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Mutat Res; 93(2):263-271 1982

The host-cell reactivation of irradiated Herpes simplex virus Type I (MacIntyre strain) (HSV1) baby hamster kidney (BHK) cells was compared to that of mammalian cells previously shown to be efficient in this process: normal human fibroblasts (HF) and UV-repair-deficient xeroderma pigmentosum (XP) cells. BHK cells had an intermediate ability to reactivate UV-damaged virus (HF greater than BHK greater than XP). BHK cells were more proficient at DNA repair than mouse L929 fibroblasts when UV dose as low, but were less capable than mouse cells at higher doses. HF and BHK were similar to each other in reactivation of gamma-irradiated HSV1 but XP cells were somewhat less efficient than the other two types. UV treatment of BHK cells 0-48 hr prior to infection with HSV1 enhanced the reactivation of the virus. The relationship between bacterial excision repair and reactivation of virus by mammalian cells is discussed. (35 Refs)

29. QUANTITATIVE STUDIES ON BLEOMYCIN-INDUCED STRAND BREAKAGE OF CHROMATIN DNA.

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Okayama Igakkai Zasshi; 93(3/4):361-381 1981

Single and double strand breakage of DNA by bleomycin under various conditions was analyzed quantitatively using purified simian virus 40 (SV40) DNA and SV40 chromatin. The method employed for DNA assay was fluorometry of SV40 DNA separated into three forms I, II, and III by 1.4% agarose gel electrophoresis and stained with ethidium bromide. This method was extremely simple and accurate for quantitative estimation of single and double strand breakage of circular DNA. The amount of bleomycin required for in vitro breakage of SV40 chromatin DNA was much higher than that of naked SV40 DNA. 2-Mercaptoethanol accelerated bleomycin-induced DNA strand breakage. The concentration of 2-mercaptoethanol required for the acceleration was higher in SV40 chromatin than in SV40 DNA. DNA strand breakage was induced by ferrous ions in the absence of bleomycin to a similar level in SV40 chromatin and in SV40 DNA. The acceleration of bleomycin-induced strand breakage by a low concentration of ferrous ion was higher in SV40 DNA than in SV40 chromatin. Ethylenediamine tetraacetic acid (EDTA) and copper ions were not efficient for stopping the reaction of bleomycin-induced DNA breakage. Sodium dodecyl sulfate (SDS) was a useful reagent for stopping the reaction. (Author abstract) (75 Refs) (In JPN)

30. MECHANISM FOR THE LOSS OF PREFERENTIAL BENZO[A]PYRENE BINDING TO THE LINKER DNA OF CHROMATIN.

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Carcinogenesis; 3(3):341-344 1982

We have examined the fate of the asymmetric chromosomal distribution of DNA adducts generated by the chemical carcinogen r-7,t-8-dihydroxy-t-9,10-oxy-7,8,9,10 tetrahydrobenzo[a]pyrene (BPDE). Treatment of mouse embryo cells with BPDE results in 3.5x more binding to the linker DNA regions between nucleosome cores than to the nucleosome core DNA itself, but 24 hr post-treatment incubation of these cells leads to a loss of this non-random binding. A similar result was obtained when post-treatment incubation was carried out in the presence of hydroxyurea indicating that factors other than DNA replication are responsible for this change in adduct distribution. However in the case of excision repair deficient xeroderma pigmentosum (XP12/BE) cells the non-random adduct distribution was stable over a period of 48 hr, whereas with excision repair proficient XP variant (XP4/BE) cells, loss of preferential binding did occur. These results indicate that the loss of non-random nucleosomal DNA modification with time can be accounted for by the preferential removal of adducts from micrococcal nuclease sensitive linker DNA and further, demonstrates that in certain cells at least, the relative position of nucleosome core structures on DNA remains unchanged over a period of at least 48 hr. (Author abstract) (18 Refs)

31. NUCLEOSOME SEGREGATION AT A DEFINED MAMMALIAN CHROMOSOMAL SITE.

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Proc Natl Acad Sci USA; 79(6,part1):1810-1814 1982

When animal cells replicate chromatin under conditions precluding new histone biosynthesis, half of the daughter DNAs are devoid of nucleosomes and are sensitive to staphylococcal nuclease. DNA sequences resistant to nuclease are associated with preexisting nucleosomes, which redistribute to progeny DNA duplexes during replication. We labeled newly replicated DNA sequences in a simian virus 40 (SV40)-transformed Chinese hamster cell clone with 5-bromodeoxyuridine (BrdUrd) in the presence and absence of a protein biosynthesis inhibitor, emetine. We resolved single-stranded BrdUrd- and dT-DNA sequences protected from nuclease digestion by nucleosomes and determined from which strands of the integrated viral DNA parental template (dT) and newly replicated progeny (BrdUrd) sequences were derived. Because we knew that the cell clone studied contained all of its integrated SV40 DNA at a single chromosomal site, we were able to determine that preexisting nucleosomes segregated to only one of the two daughter duplexes containing the integrated viral sequence. Additionally, in the presence of emetine, the integrated viral origin of replication, ORIsv, appeared not to function as a chromosomal replication origin, perhaps reflecting the drug's effect on synthesis of SV40 large tumor antigen. (Author abstract) (20 Refs)

32. DIFFERENT HISTONE FAMILIES IN INTRACELLULAR SV40 NUCLEOPROTEIN COMPLEXES WITH RESPECT TO THE ACETYLATION TURNOVER.

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Virology; 118(2):389-400 1982

The turnover of normal and butyrate-induced acetylation in the histones complexed with intracellular SV40 DNA was analyzed in infected CV-1 cells. The analysis concerned the two principal structures containing the intracellular SV40 chromatin: the 75 S complexes and the provirions. It was found that, while the normal acetylation in the 75 S chromatin turns over a lower rate than that of the host-cell chromatin, the hyperacetylation induced by butyrate turns over a rate very close to that of cell chromatin. This distinguishes two families of 75 S histones, presumably corresponding to nucleosomes with different accessibility to histone-modifying enzymes. A third type of turnover is shown by the provirion histones, in which the normal acetylation occurs at a low rate but is highly conserved. The response to butyrate in these structures is either absent or similar to that of the 75 S histones. In the chromatin of the late SV40 mutant tsB11, histone hyperacetylation does not occur when infection proceeds at the restrictive temperature for the coat-protein assembly. The hyperacetylation of histones which characterizes the morphogenesis of SV40 appears to be an assembly-dependent process, starting in the 75 S chromatin and building up mainly in the provirions. (Author abstract) (38 Refs)

EFFECTS OF EXOGENOUS AGENTS ON CHROMOSOMES

33. ELEVATED SISTER CHROMATID EXCHANGE (SCE) RATE IN PATIENTS WITH SUN-INDUCED SKIN TUMORS.

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Arch Dermatol Res; 272(1/2):151-153 1982

Effects of the spontaneous sister chromatid exchange (SCE) and the UV chemical rays (UVC)-induced increase of SCE in peripheral leukocytes at risk for actinic keratosis and sun-induced malignancies were studied. SCE with and without UVC irradiation was studied in vitro in peripheral leukocytes of 21 patients with sun-induced, non-melanoma skin tumors (actinic keratoses, basal cell and prickle cell carcinomatas) and compared with a control group of 21 healthy volunteers of the same age (30-75 yr old). The mean values and the standard deviations are shown. In the non-melanoma tumor group the spontaneous SCE and the light-stimulated increase of the phenomenon is significantly higher than in the melanoma group. SCE is currently being used to determine spontaneous and induced mutagenic and carcinogenic effects on chromosomes and cells. SCE are positively correlated with the mutation rate and are compatible with the cell survival. The higher SCE in patients with sun-induced non-melanoma skin tumors evidences an elevated somatic mutagenicity in leukocytes and rises the question whether this is an additional risk factor, completing the risk spectrum to be established. Non-melanoma and melanoma groups behave differently regarding the degree of SCE elevation and DNA repair activity in leukocytes. (8 Refs)

34. SERIAL ANALYSIS OF CHROMOSOMAL ABERRATIONS AND PROLIFERATION KINETICS OF MOUSE SPERMATOGONIA AFTER SINGLE OR FRACTIONATED X-RAY EXPOSURES.

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Mutat Res; 93(2):419-437 1982

X-ray-induced chromosomal aberrations were studied in dividing spermatogonia of 10-15 wk old male Swiss random-bred (Cpb(SE)S) mice. Single doses of 50, 100, and 150 rad were followed by examination of cytogenetic effects continuously from 4-48 hr after irradiation, together with bromodeoxyuridine (BrdU) labeling of spermatogonial chromosomes in vivo to provide cell kinetics after irradiation. A fractionation experiment was also performed (100+ 50 rad, with 24-hr interval). Chromatid-type aberrations show the highest incidence for all doses at the first fixation times. The peak yield of chromosome-type aberrations occurs at about 24 hr for 50 rad, and about 30 hr for 100 and 150 rad, suggesting 6-8 hr extra mitotic delay for higher exposures. BrdU-labeling suggested an 18-hr delay in cell-cycle progression from 100-and 150-rad treatments; the discrepancy in the two methods may be explained by analysis of the rate of cell killing. A low mitotic activity was observed from 20 to 40 hr, a period of high frequencies of chromosome-type aberrations. The G2 phase is far more sensitive to chromosomal aberration production by x-rays in terms of number of breaks per cell than the G1 or S phases. None of the parameters analyzed, ie, time sequence of chromosomal aberrations, mitotic activity, and cell kinetics, exhibited a threshold effect with respect to x-ray dose, indicating the absence of sensitization. (39 Refs)

35. GENETIC DAMAGE INDUCED BY X-RAYS OR NEUTRONS IN SPERMATOZOA OF DROSOPHILA MELANOGASTER; DIFFERENTIAL PROCESSING IN THE OOCYTES OF FEMALES CARRYING THE DNA-REPAIR-DEFICIENT MUTANTS MEI-9A AND MUS-101D1.

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Mutat Res; 94(1):63-78 1982

Two DNA-repair-deficient mutants of Drosophila melanogaster, mei-9a and mus-101D1, were used to assay the specific types of DNA lesions that might be produced by specific types of irradiation, in this case x-rays vs neutrons. Irradiated Basc males were crossed to homozygous mei-9a or mus-101D1 females, or to repair-proficient control females. Frequencies of recovered sex-linked recessive lethal mutations and of II-III translocations were used to assess the effects of impaired maternal repair. From irradiated Basc males crossed to mei+ and mus+ control females, sex-linked recessive lethals were recovered at a frequency of 4.05% after x-ray treatment, against 6.44% after exposure to neutrons [relative biological effectiveness (RBE) = 1.64]. Basc males crossed to mei-9a females gave lethal frequencies of 6.32% with x-rays, 5.58% with neutrons, and 1.46% spontaneous lethals (RBE = 0.85). Neutron lesions appeared to end up as recessive lethals at a lower frequency in zygotes derived from fertilized eggs of mei-9a females in comparison with control zygotes from mei+mus+ females. Both types of radiation led to a much reduced recovery of translocation when mus-101D1 females were used; with x-rays, the induction frequency was only 1.24%, or less than half the frequency of 2.93% observed with mei+mus+ controls. With neutrons, a slightly higher value of 1.60% was observed. The pattern of effects brought about by the two mutants was different. Not only could mus-101D1 be distinguished from mei-9a by its stonger effects on the recovery of neutron-induced damage, but it also showed an end-point specific effect on translocation recovery in the x-ray experiments. (44 Refs)

36. THE INHIBITION OF DNA REPAIR BY APHIDICOLIN OR CYTOSINE ARABINOSIDE IN X-IRRADIATED NORMAL AND XERODERMA PIGMENTOSUM FIBROBLASTS.

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Mutat Res; 94(1):229-234 1982

By incubating x-irradiated human fibroblasts with or without aphidicolin (APC) or cytosine arabinoside (AraC), it was investigated (1) whether DNA polymerase alpha participates in the repair of x-ray-induced DNA damage in normal and xeroderma pigmentosum (XP) cells incapable of excising UV-induced pyrimidine dimers, and (2) whether any responses seen with APC are observed with AraC, a known inhibitor of DNA replication and DNA repair in mammalian cells. Normal fibroblasts and excision-deficient XP fibroblasts were prelabeled with [14C]- and [H3]thymidine, respectively. They were then plated in the same dishes and exposed to a range of x-ray doses prior to incubation with or without either APC or AraC. DNA was then isolated on alkaline sucrose gradients. Profiles of gradients indicated that after doses of 150 or 250 Grays the repair of a fraction of the DNA damage was inhibited in both normal and XP cells by APC or AraC. Incubations with both AraC and APC did not increase the breaks seen with either agent alone. The response to post-irradiation incubation with APC was very similar to that seen with AraC, which was also seen after UV-irradiation. It was suggested that AraC blocks both semi-conservative replication and repair replication in a way similar to that of APC, ie, by blocking DNA polymerase alpha. (12 Refs)

37. INDUCTION OF CHROMOSOME DAMAGE BY ULTRAVIOLET LIGHT AND CAFFEINE: CORRELATION OF CYTOGENETIC EVALUATION AND FLOW KARYOTYPE.

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Cytometry; 2(5):287-290 1982

The flow karyotype (FKT) of Chinese hamster cells after treatment with UV light and caffeine (CF) was investigated and the correlation between the debris in FKT and the frequency of cells with generalized chromosome shattering (GCS) and with chromosome damage were studied. A derivative (650 A) of the M3-1 Chinese hamster cell line was used. The increase in frequency of mitotic cells (MC) showing GCS and other aberrations with increasing UV exposure is presented. The percentage of MC with GCS was very low after CF treatment alone but increased drastically to almost 90% as the UV fluence increased to 7.5 Joule/square meter (J/m2). UV irradiation alone did not induce GCS (%GCS less than 1; % aberrant up to 5) in the dose range investigated. The effect of UV plus CF treatment on FKT is shown. The debris continuum in FKT of UV irradiated cells (5 J/m2) postincubated with CF increased so drastically that no clear chromosome peaks were obtained. The relative debris level in FKT is shown as a function of the UV fluence for cells treated with UV and postincubated with or without CF. While no marked increase in relative debris level was observed following UV irradiation alone or CF treatment alone, the relative debris level was increased strongly with UV fluence after the combined treatment. Microscopic examination of chromosome suspensions revealed a high frequency of chromosome fragments. Whether the observed effects are due to a high number of chromosome breaks existing prior to chromosome isolation or to an increased chromosomal fragility is not known. (22 Refs)

38. DIFFERENCES IN MURINE PROCARCINOGEN ACTIVATION ENZYMES ARE NOT ACCOMPANIED BY PARALLEL DIFFERENCES IN PROCARCINOGEN-INDUCED SISTER-CHROMATID EXCHANGE.

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Mutat Res; 94(1):143-153 1982

The correlation between sister chromatid exchange (SCE) formation and the induction of hepatic microsomal drug metabolizing enzymes was investigated. p-Chloromethylaniline demethylase activity was measured in regenerating murine liver as an index of responsiveness to induction of drug metabolizing enzymes by administration of phenobarbital (PB). This activity was inducible in both C57Bl/6 and DBA/2 mice. Constitutive enzyme levels were about the same in the two strains, as was the extent of PB induction (6-fold). 3-Methylcholanthrene did not appreciably induced demethylase activity. PB pretreatment did not influence the number of SCEs induced by cyclophosphamide (CP) in liver and bone marrow cells of hepatectomized animals. Liver and bone marrow cells showed very similar SCE formation in response to CP, even through the liver is thought to be the major site of drug metabolism. These results indicate that differences in procarcinogen activation detected by synthetic substrates are not associated with comparable differences in SCE induction. (41 Refs)

39. EVALUATION OF THE CARCINOGENIC POTENTIAL OF 2,4-DINITROFLUOROBENZENE AND ITS IMPLICATIONS REGARDING MUTAGENICITY TESTING.

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Carcinogenesis; 3(2):139-145 1982

Tumor promoters are compounds which dramatically enhance the appearance of tumors when chronically applied after an initiating dose of a carcinogen. Initiators are generally considered mutagens while promoters have previously been shown not to induce either DNA damage or mutations. 2,4-Dinitrofluorobenzene (2,4-DNFB), a compound used in the identification of N-terminal amino acids of polypeptides, has been previously reported to be a tumor promoter in mouse skin, while other investigators have found it to be a mutagen in bacteria and yeast. To investigate this apparent discrepancy, we chose to study the carcinogenic potential of 2,4-DNFB utilizing various methods available in V79 Chinese hamster cells. 2,4-DNFB exposure did not result in any unscheduled DNA synthesis, a measure of DNA excision repair, nor did it increase the frequency of sister chromatid exchanges in V79 cells either in the presence or absence of rat liver postmitochondrial supernatant (S-15). Forward mutations in V79 cells, either to ouabain or 6-thioguanine resistance, were not induced by 2,4-DNFB, in the presence or absence of S-15. 2,4-DNFB was, however, able to induce reversions in methionine-requiring E coli auxotrophs in a dose-dependent fashion. Phylogenetic differences between lower organisms and mammals may account for this discordance. 2,4-DNFB was found to inhibit metabolic cooperation, in a dose dependent manner, in V79 cells. This property has previously been shown to be correlated with tumor promoting ability in mouse skin. Therefore, we conclude that the carcinogenic potential of 2,4-DNFB might reside in its ability as a tumor promoter and not as a carcinogenic initiator. Furthermore, these studies serve to illustrate the need for caution when extrapolating bacterial data for risk assessment in humans. (Author abstract) (42 Refs)

40. CLASTOGENIC EFFECT OF CHROMIUM ON HUMAN LYMPHOCYTES IN VITRO AND IN VIVO.

Stella M, Montaldi A, Rossi R, Rossi G, Levis AG
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Mutat Res; 101(2):151-164 1982

Induction of sister-chromatid exchanges (SCE) and chromosome aberrations in human lymphocytes treated in vitro with Cr(VI) (K2Cr2O7) and Cr(III) (CrCl3) was examined. Cr(VI) produced a delay of cell cycle in cultured lymphocytes reflected by an increased frequency of cells in generation 1, and a parallel reduction of cells in generation 3 metaphases. Cr(III) slowed down the cell cycle at very high concentrations [10-100x greater than Cr(VI) concentrations]. Cr(VI) significantly increased the frequency of isochromatid gaps and total chromatid-type aberrations at concentrations greater than 2.5 x 10(-7) M. At doses of 5 x 10(-5) M or more, Cr(III) produced increased frequencies of isochromatid gaps and chromosome aberrations. Cr(VI) produced a dose-dependent increase in SCE in both lymphocytes in G0 and those stimulated by phytohemagglutinin that entered the mitotic cycle. Mean values of SCE/metaphase for Cr(VI) concentrations of 5 x 10(-8) M and 5 x 10(-6) M were 9.70 and 13.80, respectively, for the former group and 15.53 and 19.34, respectively, for the latter group. The effect of Cr(VI) on the induction of SCE depended on the period of the mitotic cycle at which it was applied: intervals between 27 and 24 hr and 6 and 3 hr before fixation were characterized by low levels of damage, while the period between 21 and 9 hr showed high activity. In lymphocytes from 12 males occupationally exposed to Cr(VI), the mean value of SCE/metaphase (8.08) was significantly increased in comparison with the mean value of the control group (6.31). (37 Refs)

41. SCE INDUCTION IN HUMAN LYMPHOCYTES BY COMBINED TREATMENT WITH ANILINE AND NORHARMAN.

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Mutat Res; 101(2):165-172 1982

The ability of aniline (AL) and norharman (NH) to induce an increase in the number of sister chromatid exchanges (SCE) was examined in peripheral blood lymphocytes from normal healthy males. After a 24 hr exposure of lymphocytes to AL (2 x 10(-3) and 10(-2) M) a very slight increase in SCE frequency was observed. After 48-hr AN treatments (10(-2) M), few if any cells were found at second mitosis. At 10(-3) and 10(-4) M AN concentrations, an increase in SCE was not apparent. Treatment with the AN metabolite p-aminophenol (10(-4) M) increased the yield of SCE. Addition of S9 mix did not result in increased SCE. Treatment of lymphocytes with AN plus NH in the presence of S9 mix increased SCE frequencies. NH plus S9 also induced an increase in SCE. The incidence of SCE decreased with increasing concentrations of AN in treatments with AN, NH, and S9 combined. Thus, AN seemed to counteract the SCE-inducing activity of activated NH. The frequency of NH-induced SCE was dose-dependent and increased with increasing concentrations of S9. Simultaneous application of NH and AN for 48 hr did not affect the NH-induced SCE frequencies. The results indicated that the addition of NH, which enhances the sensitivity of the Salmonella/microsome test, does not produce an enhancement of the sensitivity of the SCE test. (13 Refs)

42. INDUCTION OF SISTER-CHROMATID EXCHANGES BY INDIRECT MUTAGENS/CARCINOGENS IN CULTURED RAT HEPATOMA AND ESOPHAGEAL TUMOR CELLS AND IN CHINESE HAMSTER DON CELLS CO-CULTIVATED WITH RAT CELLS.

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Mutat Res; 93(2):409-418 1982

The inducibility of sister-chromatid exchanges (SCEs) in rat ascites hepatoma (AH66-B) and a rat esophageal tumor (R1) cell lines by 2-acetylaminofluorene, butylbutanolnitrosamine, cyclophosphamide, urethane, 4-aminoazobenzene, 2-methyl-4-dimethylaminoazobenzene, 3'-methyl-4-dimethylaminoazobenzene, 4-o-tolyazo-o-toluidine, benzo(a)pyrene, 7,12-dimethylbenzyl(a)anthracene, 3-methylcholanthrene, and diethylstilbestrol (DES) was studied. Six of the chemicals were used with a cell-mediated system using Chinese hamster Don-6 cells as the target cells and co-cultivated AH66-B or R1 cells as the metabolizing feeder layer. Out of 14 indirect mutagens/carcinogens tested, 11, including 5 amine derivatives, 3 azo compounds, 2 aromatic hydrocarbons and 1 steroid, induced SCEs in AH66-B and/or R1 cells. The frequency of SCEs in Don-67 cells exposed to 6 selected chemicals was substantially enhanced in the presence of AH66-B or R1 cells. For some chemicals, especially aromatic hydrocarbons, the doses required to induce SCEs in AH66-B and R1 cells were much higher than those reported for some other cell systems. Certain chemicals, eg, DES, were active inducers of SCEs in the present systems, but are known to be inactive in microbial and other test systems. The two approaches described represent simple and reliable screening assays in vitro for detection of indirect mutagens/carcinogens. (32 Refs)

43. PRELIMINARY EXPERIMENTAL CONTRIBUTION TO THE STUDY OF POSSIBLE CARCINOGENIC ACTIVITY OF TWO HERBICIDES CONTAINING ATRAZINE-SIMAZINE AND TRIFURALIN AS ACTIVE PRINCIPLES.

Donna A, Betta PG, Gagliardi F, Ghiazza GF, Gallareto M, Gabutto V
Istituto di Anatomia e Istologia Patologica, Ospedale Civile, Via Venezia n. 18, 15100 Alessandria, Italy
Pathologica; 73(1027):707-721 1981

The carcinogenicity and mutagenicity of the herbicides Fogard S and Treflan were studied in vivo in female Swiss albino mice and in vitro in human lymphocyte cultures. The active principles in Fogard S are atrazine (25%) and simazine (37.5%). The active principle in Treflan is trifiuralin (44.5%). Groups of 25 mice each received 0.25 ml of 2 ppm Fogard S or Treflan ip or sc, 13x at 3-day intervals. One animal from each group was killed every 15 days up to 7 mo. Necropsies were performed when possible on all animals. One mouse from the sc-Fogard S group, five from the ip Fogard S group, and four from the ip Treflan group were lost to cannibalism and could not be examined. Malignant lymphomas (ML) were found in three mice and mesothelioma (MT) in one mouse from the sc Fogard S group. ML was found in two mice from the ip Fogard S group. ML was found in five mice and MT in one from the sc Treflan group. ML was found in three mice and MT in three mice from the ip Treflan group. Cultures of human lymphocytes were stimulated with phytohemagglutinin and then exposed to 0.2, 0.1, or 0.05 cc of 2 ppm Treflan or 0.2, 0.05, or 0.01 cc of 2 ppm Fogard S. Fogard S did not produce abnormalities in morphology or chromosomal variations. At the higher dose, Fogard S produced a slight decrease in mitoses. Treflan produced significant decreases in the number of mitoses with increasing dose. Chromosomal abnormalities were produced in increased frequencies at the lowest dose. Results indicate a correlation between in vivo administration of either herbicide and tumor formation, as well as a correlation between in vitro Treflan administration and genetic abnormalities. (23 Refs)

44. CLASTOGENIC ACTIVITY OF BILE ACIDS AND ORGANIC ACID FRACTIONS OF HUMAN FECES.

Barnes WS, Powrie WD

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Cancer Lett; 15(3):317-327 1982

Clastogenic activity in bile acids and in the acid fractions (AF) of saponified chloroform-methanol extracts (CME) from human fecal matter (FM) is reported. AF of saponified CME from four human donors were studied. With AF of FM from subjects A and B, frequencies of aberrant metaphases and exchanges were considerably higher than those for the control. The C and D AC also brought about a slight elevation in aberrations. The addition of S9 mix did not enhance the clastogenic activities of AF. With hexane extracts, no detectable increase in frequency of chromosome aberrations above control values were observed, either with or without the addition of S9 mix. When five of the major bile acids were assayed, cholic acid induced a slight increase in aberration frequency and ursodeoxycholic acid (UDCA) a much larger one. Addition of S9 enhanced the increase, but the presence of S9 was not a necessary condition for the demonstration of clastogenic activity. S9 also decreased the concentration of bile acid necessary to produce chromosome damage. Experiments using the standard S9 mix containing all cofactors, the standard S9 mix without NADPH, and an S9 mix with all cofactors in which the microsomal protein had been coagulated by heating to 80 C for 3 min, were performed. UDCA induced a large number of exchanges in conjunction with all S9 mixes, and while small differences attributable to treatment exist, the activity of NADPH-requiring mixed function oxidases is not necessary. The heat-treated S9 mix increased the toxicity and the frequency of exchanges relative to control. (31 Refs)

45. CHARACTERIZATION OF SISTER CHROMATID EXCHANGE INDUCTION BY HYDROGEN PEROXIDE.

Speit G, Vogel W, Wolf M

Abteilung Klinische Genetik, Oberer Eselsberg, D-7900 Ulm, W. Germany

Environ Mutagen; 4(2):135-142 1982

The relationship between the antimutagenic action of cysteine and interaction directly with hydrogen peroxide or the free radicals produced was studied in V-79 Chinese hamster cells. In vitro exposure to H202 leads to genetic damage as evidenced by increase in sister-chromatid exchanges, which was not reduced in the presence of cysteine. The study indicates that thiol compounds do not protect against H202 activity by a direct effect, but by other reactions. (29 Refs)

46. INDUCTION OF SISTER CHROMATID EXCHANGES AND INHIBITION OF CELLULAR PROLIFERATION IN VITRO. I. CAFFEINE.

Guglielmi GE, Vogt TF, Tice RR

(c/o Tice) Medical Dept., Brookhave Natl. Lab., Upton, NY, 11973

Environ Mutagen; 4(2):191-200 1982

The ability of caffeine to induce sister-chromatid exchanges (SCEs) and to inhibit cellular proliferation of human lymphocytes in vitro was examined. Caffeine (0.10-4.10 milli(m)M) inhibited cellular proliferation in phytohemagglutinin-stimulated lymphocytes exposed continuously, but not in those receiving an acute 4-hr exposure. Administration of caffeine throughout the culture period induced a significant dose-dependent increase in SCEs, but exposure for 4 hr prior to the DNA synthetic period did not change SCE frequency. Using a linear regression curve derived from least squares analysis of the semilogarithmic plot of rate of SCE induction, the caffeine concentration capable of doubling the control SCE frequency was calculated as 2.4 mM. SCE induction rate in each of three bromodeoxyuridine replication cycles was the same. The mechanism for the results reported here is probably inhibition of DNA synthesis. Inhibition of DNA synthesis by caffeine may involve purine metabolism, transport, and salvage utilization in a direct or an indirect manner. The non-linearity of the SCE dose response curve for caffeine is in contrast to the typical linear graph for other well-known mutagenic/carcinogenic agents, suggesting that there is more than one mechanism of SCE induction. (52 Refs)

47. ANAPHASE ABERRATIONS: A MEASURE OF GENOTOXICITY IN MUTAGEN-TREATED FISH CELLS.

Kocan RM, Landolt ML, Sabo KM

Dept. Pathology, SM-30, Univ. Washington, Seattle, WA, 98195

Environ Mutagen; 4(2):181-189 1982

A continuous culture line of rainbow trout gonad (RTG-2) cells was exposed to benzo(a)pyrene (BAP), 3-methylcholanthrene (3MC), anthracene, 1-naphthol, 9-aminoacridine (9AA), mitomycin C (mit-C), and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). During exposure cells were examined for the presence of abnormalities in chromosome arrangement of anaphase figures during mitosis, and were compared to the effects of only solvent (dimethylsulfoxide). Both BAP and 3MC elevated the number of anaphase abnormalities, with more effect at 48 hr than at 24 hr. MNNG, mit-C, and 9AA were also effective in increasing the number of abnormalities. Abnormalities included mainly attached fragments, acentric fragments and bridges, with some side-arm bridges and multipolar cells. Toxicity and inhibition of cell division were also observed with all compounds. No increase in chromosomal lesions was observed in cells treated with naphthol or anthracene, suggesting that each chemical's characteristics, not the chemical class to which it belongs, are important in mutation induction. The in vitro RTG-2 cell system has a highly active mixed function oxygenase system, which eliminates the need for microsomal supplement. This test system is comparable to the Ames test and the sister-chromatid exchange test in sensitivity for measuring chromosome damage. (38 Refs)

48. INDUCED CHROMOSOME LOSS FOLLOWING TREATMENT OF POSTMEIOTIC CELLS OF THE DROSOPHILA MELANOGASTER MALE WITH MMS AND DMN AND MATINGS WITH REPAIR-PROFICIENT FEMALES AND REPAIR-DEFICIENT FEMALE MEI-9A AND ST MUS302.

Zimmering S
Div. Biology and Medicine, Brown Univ., Providence, RI, 02912
Mutat Res; 94(1):79-86 1982

Frequencies of complete and partial loss of the Y chromosome in Drosophila melanogaster ring-X males treated with methylmethanesulfonates (MMS) or dimethylnitrosamine (DMN) and mated with repair-proficient females or the repair-deficient females, mei-9a and st mus302, are reported. When males were treated with MMS and mated with the repair-deficient females, significant enhancement of induced complete loss (CL) and partial loss (PL) above controls was observed. Frequencies of induced loss were 10x higher with st mus302 than mei-9a. The same trends were observed with DMN. It was observed that st mus302 females were equally sensitive to MMS and DMN-induced break/pre-break lesions, while mei-9a females were less sensitive to MMS- than to DMN-induced lesions. Of 37 PLs observed in the mei-91 series, 13 were mosaics; of 50 with st mus 302, only one was a mosaic. The same phenomenon was observed for procarbazine and diethylnitrosamine (DEN). St mus302 females were more sensitive than mei-9a females and markedly more sensitive than repair-proficient females regarding the recovery of CLs and PLs in tests of procarbazine, DEN, MMS and DMN. Frequencies of chromosome loss are substantially higher with MMS and DMN than procarbazine and DEN. (6 Refs)

49. DNA DAMAGE IN LIVER, KIDNEY, BONE MARROW, AND SPLEEN OF RATS AND MICE TREATED WITH COMMERCIAL AND PURIFIED ANILINE AS DETERMINED BY ALKALINE ELUTION ASSAY AND SISTER CHROMATID EXCHANGE INDUCTION.

Parodi S, Pala M, Russo P, Zunino A, Balbi C, Albini A, Valerio F, Cimberle MR, Santi L
Dept. Oncology, Istituto Scientifico per lo Studio e la Cura del Tumori, 16132 Genoa, Italy
Cancer Res; 42(6):2277-2283 1982

Aniline of unknown purity has been reported to induce spleen hemangiosarcoma in rats. Aniline has been found to be negative in terms of mutagenicity in both bacteria and yeasts. We have found that both commercial (already rather pure) and repurified aniline are clearly positive to a similar extent in inducing DNA damage in vivo in liver and kidney of rats. Both the commercial and repurified product are also clearly positive in induction of sister chromatid exchanges in vivo in male Swiss mice bone marrow cells. Liver, kidney, and bone marrow DNA damage was absent in male Swiss mice. (Author abstract) (30 Refs)

50. MUTAGENIC EVALUATION OF MORPHINE SULPHATE AND PETHIDINE HYDROCHLORIDE IN MICE BY THE MICRONUCLEUS TEST.

Das RK, Swain N
Sch. Life Sciences, Sambalpur Univ., Burla 768017, India
Indian J Med Res; 75:112-117 1982

Mutagenicity of morphine sulfate (MS) and pethidine hydrochloride (PH) was evaluated in vivo by the micronucleus test in mice. The animals were treated ip with various doses of either MS or PH twice with an interval of 24 hr. At 6 hr after the second treatment they were killed and bone marrow smears were prepared. Polychromatic and normochromatic erythrocytes and nucleated cells were examined for the occurrence of micronuclei. Distilled water treated individuals served the purpose of control. The erythrocytes showed significant increase in the incidence of micronuclei at all the dose levels tested for both the drugs, which clearly indicated chromosome breaking ability of the narcotics. Comparative analysis of the data for the two drugs exhibited slightly higher effectiveness of morphine in producing micronuclei. Importance was not attached to the incidence of micronuclei in the nucleated cells because of some doubt in scoring. The chromosome breaking activity of the narcotics and their probable modes of action have been discussed. (Author abstract) (21 Refs)

51. ANTIMUTAGENIC EFFECT OF ALPHA-TOCOPHEROL ACETATE DURING CARBON TETRACHLORIDE POISONING.

Maganova NB, Stasenkova KP, Bondarev GI
Inst. Nutrition, Moscow, USSR
Vopr Pitan; (1):44-47 1982

The antimutagenic effect of alpha-tocopherol acetate (ATA) was studied in C57BL/6 mice and Wistar rats subjected to acute, subacute, and chronic exposure to carbon tetrachloride (CTC). Daily ATA administration to animals subjected to acute and subacute po exposure to CTC did not affect the incidence of chromosome aberrations in the bone marrow cells. ATA administration to animals subjected to inhalation exposure to CTC produced a significant decrease of the frequency of chromosome aberrations and significant decrease of the frequency of dominant lethals in germ cells. (11 Refs) (In RUS)

52. EVALUATION OF CHEMICALLY INDUCED CYTOGENETIC LESIONS IN RABBIT OOCYTES. II. A COMPARISON OF STREPTONIGRIN EFFECTS ON SOMATIC AND GERM CELLS.

DuFrain RJ, Littlefield LG, Wilmer JL, Frome EL
Radiation Emergency Assistance Center/Training Site, Medical and Health Sciences Div., Oak Ridge Associated Universities, P. O. Box 117, Oak Ridge, TN, 37830
Mutat Res; 94(1):103-114 1982

Effects of streptonigrin (STN) on somatic and germ cells of New Zealand white rabbits were investigated. Cytogenetic findings in bone-marrow cells and lymphoblasts from the mesenteric lymph nodes were reported and inherited structural chromosome aberrations in day-6 blastocysts obtained from female rabbits treated with graded doses of STN prior to mating were studied. A single statistical methodology was applied in the individual dose-response determinations so that the coefficients of dose for the different cell types were comparable. Cytogenetic damage in the oocytes was measured by the incidence of inherited aberrations assessed in karyotype preparations from 361 6-day blastocysts obtained from 55 rabbits. Cytogenetic damage was assessed in lymphocytes and bone marrow cells collected 6 hr after initiation of STN dosing. STN injections in the dose range of 30-90 ug/kg given to sexually mature females caused dose-dependent increases in chromosome aberrations in both types of somatic cells and in the incidence of inherited aberrations recovered in 6-day blastocysts. For blastocysts, bone marrow, and lymphoblasts, respectively, the coefficients of damage recovered in blastocysts vs damage recovered in somatic cells were in the ratio of 1:2.3:5.8, indicating overestimation by factors of 2.3 to 5.8, respectively, in bone marrow and lymphoblasts, the incidence of inherited structural aberrations recovered in preimplantation embryos. Somatic cell cytogenetic damage is in some way predictive of damage incurred by oocytes which can be passed on to preimplantation embryos, for agents such as STN. (29 Refs)

53. ALTERED CELL CYCLE PROGRESSION AND ABERRANT MITOSIS IN ADENOVIRUS-INFECTED RODENT CELLS.

Murray JD, Bellett AJ, Braithwaite AW, Waldron LK, Taylor IW
Ludwig Inst. Cancer Res., Sydney, Univ. Sydney c/o Taylor, Sydney N.S.W. 2006, Australia
J Cell Physiol; 111(1):89-96 1982

It is reported that human adenovirus type 5 (Ad5) caused alterations in the cell cycle of some growing rodent cells, and that the induction of chromosome damage was cell-cycle dependent and required the expression of one or more early viral genes. Temperature sensitive mutants of Ad5 were found incapable of viral DNA replication and hence gene expression at not permissible temperatures without affecting chromosome damage; this damage must thus result from expression of one or more of the early viral genes. Ad5-infected cells suffered mitotic abnormalities that affected cells suffered mitotic abnormalities that affected segregation of chromosomes and cytokinesis as well as structural aberrations in the chromosomes. Chromosome damage was higher in all Ad5-infected samples than in mock-infected controls. Cyclic variations in virus-induced damage occurred with peaks averaging 22 hr apart. The av total cell cycle time calculated for mock-infected cells was 26 hr and for Ad5-infected cells 20 hr. G2, M and S phases were approximately the same for the two populations. Differences in cell cycle time were therefore due to differences in the length of F1, which was approx 5 hr in control cells and 0.5 hr in Ad5-infected cells. (26 Refs)

GENERAL REVIEWS

54. CANCER 1980: ACHIEVEMENTS, CHALLENGES, AND PROSPECTS.

Clark RL
Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Cancer; 49(9).1739-1745 1982

This review article touches on various categories of research that have been expanded or made possible predominantly by funding through the National Cancer Program of the National Cancer Institute and the American Cancer Society. Under diagnosis, categories mentioned are biological markers, chromosome banding techniques, fluorescent-activated cell sorter identification of cell surface antigens, ultrastructural studies with electron microscopy, histochemical, radiologic, ultrasonographic, thermographic, angiographic techniques, nuclear magnetic resonance imaging, radioactivity labeled compounds that attach to specific tumor cell surface receptors, and other agents that are preferentially taken up by tumor tissues. Predictive tests include human tumor stem cell assays, sister chromatid exchange assay, and hormone receptor assays. The techniques listed under therapy include hyperthermia, immunotherapy, chemotherapy, radiosensitizing compounds, and the supportive measures of hyperalimentation and other nutritional manipulations, psychological reinforcement, rehabilitative efforts, bone marrow transplants, blood component therapy, protective 'germ-free' environments, and pain control. Drug delivery systems, animal and cell culture models, and prevention of carcinogenesis are also mentioned. (Author abstract) (71 Refs)

55. PRINCIPLES OF CANCER BIOLOGY: CELL BIOLOGY AND BIOCHEMISTRY OF CANCER.

Pardee AB
Div. Cell Growth and Regulation, Sidney Farber Cancer Inst., Harvard Medical Sch., Boston, MA
Cancer - Principles and Practice of Oncology. DeVita VT, Hellman S, and Rosenberg SA, ed. Philadelphia, Lippincott, 1926 pp., 1982.

No differences between malignant and nonmalignant cells have yet been discovered which can serve as a basis for a universally accepted therapy. Recent research in cell biology, tissue culture, biochemistry, and cell genetics may help to provide answers for the somewhat more specific questions. Questions such as: growth factors required by normal and neoplastic cells, the biochemical mechanisms which determine cell number increases or non-growth, the numbers and chromosomal locations of 'cancer' genes, the cause(s) and significance of the rapid appearance of chromosomal changes in cancer cells, the basis of anaplastic morphologic and biochemical differentiation in cancer cells, the roles of surface, membrane, and cytoplasmic structure changes in neoplasia, and the role of error-prone DNA repair in tumorigenesis and drug resistance, can now be asked. Current cancer therapy is an attempt at selective cell killing, based upon the greater growth fraction of cancer cell populations. It is possible that in the early stages of tumor progression, the difference between tumor-forming and non-tumor-forming cell populations may be small and quantitative. Further research is needed to define these differences and exploit them for treatment and prevention. (153 Refs)

56. CYTOGENETICS OF PRELEUKEMIA.

Nowell PC
Dept. Pathology, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
Cancer Genet Cytogenet; 5(3):265-278 1982

A summary is presented of the major cytogenetic findings in various hematopoietic disorders that carry an increased risk for leukemia, with emphasis on the more recent results with banding techniques. Groups of disorders discussed include cytopenic disorders (dysmyelopoietic syndromes, DS) (DS with specific chromosome changes, cytogenetic evolution and progression to leukemia, cytopenic preleukemia in patients previously treated for malignant disease, prognostic value of chromosome studies in cytopenic preleukemia); myeloproliferative disorders (MD) (prognostic value of chromosome studies in MD); and preleukemic disorders of childhood (clinical value of chromosome studies in childhood preleukemia). Biological significance of chromosome changes in preleukemia is considered. Some evidence suggests that chromosome studies may be of prognostic value in DS; patients with abnormalities show decreased survival time and are at increased risk for progression to ANLL (acute non-lymphocytic leukemia). Karyotypic findings in the preleukemias suggest that the various clinical disorders are a group of related diseases derived from an altered hemic stem cell. (61 Refs)

57. CELL LINEAGES IN HEMATOPOIETIC NEOPLASIA STUDIED WITH GLUCOSE-6-PHOSPHATE DEHYDROGENASE CELL MARKERS.

Fialkow PJ
Dept. Medicine, Univ. Washington, Seattle, WA, 98195
J Cell Physiol; Suppl1:37-43 1982

The indirect method based upon study of hematologic neoplasms arising in females whose X-chromosomes inactivation mosaicism is delineated with glucose-6-phosphate dehydrogenase (G6PD) markers is reviewed. Chronic myelogenous leukemia (CML), lymphocytes in CML, significance of Philadelphia chromosome (Ph), agnogenic myeloid metaplasia with myelofibrosis, other myeloproliferative disorders, acute nonlymphocytic leukemia (ANLL), chronic lymphocytic leukemia, applications of the G6PD system to the study of hematologic cell regulation in neoplasia, and potential applications of the G6PD system to the study of long-term hematologic cell cultures are discussed. Several types of investigations indicate that cells of CML clone differentiate into B-lymphocytes. The G6PD findings in lymphocytes in patients with CML indicate the existence of similar stem cells to those in rodents and that CML involves a stem cell pluripotent for lymphocytes as well as for myelogenous cells. Studies of G6PD and chromosomes in B-lymphoblastoid cell lines established from a patient with Ph-positive leukemia who was heterozygous for G6PD provide evidence for the existence of cells derived from the abnormal clone that are Ph-negative. Thus, acquisition of Ph may not be sufficient cause for the disease. Eight G6PD heterozygotes with ANLL have been studied. Only a single-enzyme G6PD phenotype was found in the leukemic blast cells, suggesting that the disorders in these patients were clonal. In the patients who were studied when their disease entered remission, a return to normal double-enzyme phenotype in granulocytic cells was observed. (47 Refs)

58. INSERTION OF DRUG RESISTANCE GENES IN ANIMALS.

Bar-Eli M, Mercola KE, Slamon DJ, Mauritzson N, Stang HD, Cline MJ
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J Cell Physiol; Suppl1:213-217 1982

Techniques for inserting new genetic information into animal cells, chromosome-mediated transfer of genetic information (CMTGI), microcell-mediated transfer, DNA-mediated transformation, direct injection of new genes, use of viral vectors to insert new genes, insertion of new genetic information into adult animals, methotrexate (MTX)-resistant dihydrofolate reductase (DHFR), inhibition by MTX, and polyacrylamide gel analysis are discussed. CMTGI technique utilizes isolated metaphase chromosomes as vectors for the transfer of genetic information. Microcells are single chromosomes or small groups of chromosomes contained within a nuclear membrane. Techniques also exist for isolating microcells from cells that grow in suspension culture rather than adherent to surface. A method utilizing cellular endocytosis of calcium microprecipitates of DNA has been used to insert highly purified DNA sequences containing specific genes. Genetic material can be injected directly into the nucleus of cells. Modified SV-40 has been used as a vector to introduce cloned genes into mammalian cells. Discrete portions of the SV-40 viral genome have been covalently linked to specific prokaryotic and eucaryotic genes and used in DNA-mediated transformation experiments. Experiments aimed at inserting new genes into the bone marrow cells of living mice based on previous studies in tissues culture were performed. Three mechanisms of resistance have been identified: mutations affecting intracellular transport of drug, mutations that alter the affinity of DHFR for MTX, and reduplication of presumably normal DHFR gene resulting in increased rates of enzyme synthesis and of cellular DHFR concentration. (42 Refs)

59. GENETIC INTERACTIONS BETWEEN TUMOR VIRUSES AND HOST CELLS.

Rowe WP
Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
Cancer; 49(10):1958-1962 1982

Accomplishments in the field of tumor virology over the past 25 yr are reviewed. The list of viruses known to cause tumors in nature or in laboratory systems has expanded greatly. The oncogenic viruses include retroviruses, herpesviruses, papovaviruses. Dramatic changes have taken place in the study of the genetic interactions between tumor viruses and virus-transformed cells, in searches for virus causation of tumors, and for a genetic and biochemical basis of malignant transformation. Polyoma viruses, adenoviruses, and retroviruses analyzed in mouse or hamster systems are discussed in relation to tumorigenesis. Infectious virus need not be present for tumor induction. Discoveries related to genetic interactions between viral and host cell genes in retrovirus leukemogenesis include the following: viruses produced directly from the inherited endogenous retroviral genes in the mouse are not tumorigenic; during the course of spreading infection, genetic recombinants arise between genomes of the infectious virus and the defective viral genes in the chromosomes of the host; a similar type of recombination can take place between infectious retroviruses and cellular genetic information; in B-lymphocytes transformed by avian retrovirus, only a piece of the virus genome may remain, analogous to the defective genome insertions seen with DNA tumor viruses. Other aspects of tumor virus DNA-host cellular DNA interactions are discussed. (49 Refs)

60. MOVABLE GENETIC ELEMENTS.

Watson JD
Cold Spring Harbor Lab., Box 100, Cold Spring Harbor, NY, 11724
Cold Spring Harbor Symp Quant Biol 45(part 1): 445 pp., 1981.

Inversion elements in bacteria, general properties of transposable elements in bacteria (TEB), structure and function of TEB, factors affecting transposition, mechanism of transposition, mechanism of Mu transposition, and biochemistry of recombination are reviewed. Analysis of crosses between genetically marked corn plants has led to the postulate that activity of key genes is under the control of genetic elements having the capacity to move from one chromosomal site to another. When a control element moves away from a gene, the activity of that gene suddenly reappears. Certain highly pleiotropic mutations of Escherichia coli are the result of the insertion of discrete DNA segments that can jump from one chromosomal site to another. Insertion sequences (IS) may exist not only in bacteria but also in all organisms. Closely spaced pairs of IS can move as units, carrying along the genes lying between them. Such transposons bare many similarities with the phage Mu. Some experiments have indicated that the structure of integrated retroviruses is remarkably similar to that of transposons. (1651 Refs)

61. CHROMOSOMAL METHODS IN POPULATION STUDIES.

Conner MK, Wald N
Graduate Sch. Public Health, Univ. Pittsburgh, Pittsburgh, PA, 15262
Environ Health Perspect; 42:107-113 1981

Chromosomal aberrations and sister chromatid exchanges (SCE) are described as a means for evaluating DNA damaging agents. Biological changes produced by low level radiation exposure may be detected with sensitivity, using cytogenetic aberration scoring of human blood cells. Examples of in vivo cytogenetic studies of low level radiated populations are tabulated. Adequate sample size requirements and accurate assessment of cumulative exposure effects with increased age are important for reliable cost benefit analysis of low level exposure. Implications of SCE for an individual's health or for the general public's genetic health is discussed. (40 Refs)

62. HOW DO HUMAN ISOCHROMOSOMES ARISE?

de la Chapelle A
Dept. Medical Genetics, Univ. Helsinki, Haartmaninkatu 3, 00290 Helsinki 29, Finland
Cancer Genet Cytogenet; 5(2):173-179 1982

Characteristics of isochromosomes (IC), metacentric elements formed by transverse instead of longitudinal division of the centromere, are reviewed. Both constitutional and acquired isochromosomes are described. IC are not uncommon in human leukemias and tumors. The best-known example, i(17q), occurs not only in the blastic phase of chronic myeloid leukemia, but also in many other leukemias and tumors. In contrast to congenital abnormalities, many chromosome arms may be found as IC in cancer cells. Descriptions of IC of 1q, 1p, 2p, 5p, 7q, 11q, and 16q have been found in addition to 17q. In lymphoma i(8q) and i(6p) have recently been observed. The role of misdivision of the centromere in the development of IC is discussed. The nonrandom occurrence of the various acquired IC within the karyotype may be because IC are formed with nonrandom frequency or because they lead to different consequences (selective advantage or disadvantage). Observations and interpretations are presented. (27 Refs)

OTHER RELATED STUDIES

63. HYPOTONIC DESTRUCTION UNCOVERS CHROMOSOMAL ABERRATION.

Schroder J, Grunewald B, Struck L

Institut fur Rechtsmedizin der Universitat, D-2000 Hamburg, W. Germany

Naturwissenschaften; 69(3):150 1982

Nuclei with appendages resembling drumsticks or micronuclei were discovered following hypotonic treatment of leukemic WBC in mature and immature myeloid cells from 3/5 patients with acute myeloid leukemia. The results suggested that the appendage may represent a supernumerary chromosome inactivated during interphase. Screening for nuclei with appendages following hypotonic treatment may possibly be useful in determining cell lines with certain types of chromosomal changes. (4 Refs)

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CLINICAL STUDIES OF CHROMOSOMES IN HUMAN CANCER

1. INCIDENCE OF BALANCED 9Q;22Q TRANSLOCATIONS IN THE PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA (CML) (MEETING ABSTRACT)

Dosik H, Verma RS
Department of Medicine, The Jewish Hospital and Medical Center of Brooklyn, Brooklyn, NY
Am J Hum Gen; 33(6):62A 1982

The saga of improved banding techniques is particularly interesting in relation to the Philadelphia (Ph') chromosome (22q-) whose association with chronic myelogenous leukemia (CML) was discovered by Nowell and Hungerford. This abnormal chromosome, while thought to be a deletion of the long arm of chromosome 22 has now been confirmed as a balanced translocation involving the long arm of chromosomes 9 and 22. Cytogenetic identification is usually performed either by QFQ or by GTG technique. However, by both techniques, the terminal bands of the long arm of chromosome 9 (band q34) and 22(bandq13) are stained negatively. Consequently, the

HE20.3173/2:

exact nature of this most common translocation may go undetected. We report 52 cases who had been diagnosed as Ph' positive CML by RFA technique in order to study the precise origin of the Ph' chromosome. We used RFA technique, because terminal bands are positively stained and any minor deletion can easily be detected. Ninety percent cases had 9q;22q translocation, 4% had unusual and 6% cases were without any translocation. The breakpoints were variable on the long arm of chromosome 22 and four types of Ph' chromosomes were recognized. The incidence of very large, large, average and small were 1.92%, 3.85%, 80.77% and 13.46% respectively. (no Refs)

2. IDENTIFICATION OF THE CONSTANT CHROMOSOME REGIONS INVOLVED IN HUMAN HEMATOLOGIC MALIGNANT DISEASE.

Rowley JD
Dept. Medicine, Univ. Chicago, Chicago, IL, 60637
Science; 216(4547):749-751 1982

Specific consistent chromosome translocations are regularly observed in certain human leukemias and lymphomas. For the myeloid leukemias, the constant recombinants are: the long arm of 9 to chromosome 22 in chronic myeloid leukemia, the long arm of 21 to chromosome 8 in acute myeloblastic leukemia, and the long arm of 17 to chromsome 15 in acute promyelocytic leukemia. Three related translocations are seen in Burkitt lymphoma and B cell acute lymphocytic leukemia; in each one, chromosome 8 is involved with chromosome 2, 14, or 22. Analysis of a complex translocation affecting chromosomes 8 and 14 indicates that the translocation of chromosome 8 to chromosome 14 is the critical constant rearrangment. The analysis of the DNA at the translocation sites of these chromsomes, rather than the reciprocal of each translocation, appears to be the most productive focus for initial study. The various immunoglobulin loci are located on chromosomes 2, 14, and 22, the chromosomes regularly involved in translocations in Burkitt lymphoma and B cell acute lymphocytic leukemia. (Author abstract) (30 Refs)

3. BONE MARROW TRANSPLANTATION FOR CHRONIC MYELOGENOUS LEUKEMIA (CML) IN CHRONIC PHASE (MEETING ABSTRACT)

Champlin R, Gale RP
University of California Los Angeles Medical Center, Los Angeles, CA, 90024
Proc Am Soc Clin Oncol; 1:C-483 1982

All therapeutic interventions including marrow transplantation have been largely unsuccessful in patients with blast crisis. Seven patients with CML in chronic or accelerated phase received high dose combined modality therapy with allogeneic bone marrow transplantation from an HLA (human leukocyte antigen) identical sibling donor. Three patients were in stable chronic phase. Three had developed 'accelerated phase' with increasing organomegaly, anemia, thrombocytopenia and refractoriness to chemotherapy. One had achieved a 2nd chronic phase after treatment for blast crisis. Cytogenetic studies revealed the typical Ph' chromosome in all patients, with further clonal evolution in 2 prior to transplantation. Pretreatment characteristics included median age 24(5-37)y, interval from diagnosis to transplant 4.4(1.2-4.7)y, peripheral blood counts (x10(9)/l):granulocytes 10.9(2.7-65), platelets 252(10-880) and hematocrit 36.3(32-46)%. All patients received cyclophosphamide 120 mg/kg, total body radiation 10Gy and bone marrow transplantation. Methotrexate was administered for the first 101 days post transplant. All had prompt engraftment and 6 remain alive in unmaintained hematologic remission with normal cytogenetics 2 to 17 m post transplant. Two patients had moderate graft versus host disease. One had transient idiopathic pulmonary infiltrates. One patient relapsed and died with blast crisis 7 m post transplant. All other patients survive with a normal performance status. (no Refs)

4. C-HETEROCHROMATIN REGIONS IN CHROMOSOMES OF HEMATOPOIETIC CELLS IN LEUKEMIA PATIENTS.

Pogorelov VM, Saralidze EG, Ul'ianov NB, Kaminir LB, Kozinets GI
Lab. Hemocytology and Experimental Chemotherapy of Leukemias, Central Inst. Hematology and Blood Transfusion, Moscow, USSR
Probl Gematol Pereliv Krovi; 27(3):28-33 1982

The results of differential staining of metaphase chromosomes of the peripheral blood lymphocytes from 36 patients with various lymphoproliferative diseases are reported. A modified C-banding technique allowed identification and C-heterochromatin region and thus the differential diagnosis of leukemia. (21 Refs) (In RUS)

5. CHROMOSOME ANOMALY IN REFRACTORY ANEMIA AND LEUKEMIA PATIENTS (MEETING ABSTRACT)

Bardhan S, Samad F, Hardy R
Division of Medical Genetics, Meharry Medical College, Nashville, TN, 37208
Am J Hum Gen; 33(6):61A 1982

Blood and bone marrow of eleven leukemia and six refractory anemia patients were chromosomally analyzed by QFQ staining technique. Three cases of chronic myelogenous leukemia (CML) showed chromosome anomalies such as one with 46, XY, t(9q+22q-), another with 46, XX, t(6q+;22q-) and the third with 46, XX/47, XXX mosaicism. The latter two types of anomalies are reported for the first time. A case of acute lymphocytic leukemia (ALL) showed loss of chromosome 22 and presence of a marker chromosome. The acute myelomonocytic leukemia (AMML) had two extra marker chromosomes and a loss of a chromosome Y. One case of refractory anemia had sex chromosome mosaicism, 46, XX/47, XXX. Significance of chromosomal anomaly in refractory anemia and leukemia will be discussed. (no Refs)

6. CHROMOSOMES AS A PROGNOSTIC FACTOR (PF) IN CHILDREN AND ADOLESCENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) (MEETING ABSTRACT)

Grossi M, Kowalczyk J, Suh O, Minowada J, Brecher ML, Green DM, Freeman AI, Sandberg A
Roswell Park Memorial Institute, Buffalo, NY, 14263
Proc Am Soc Clin Oncol; 1:C-527 1982

The importance of chromosome findings as a PF in ALL was studied by statistical analysis among 42 patients diagnosed between 1970 and 1979. All patients received the same induction therapy. For the sanctuary phase, 26 patients received intermediate dose methotrexate (IDM) (500 mg/m2 x 3); 11 patients received IDM x 3 followed by high dose methotrexate (1500 mg/m2 x 3); 5 other patients received cranial irradiation (3) or cytoxan (2). All patients had the same maintenance therapy except for those who received cytoxan. Known PF such as age, initial WBC, platelets, hemoglobin, bone marrow status on day 28 of induction therapy, liver size, spleen size, node size, FAB morphological classification and cell surface markers were compared against chromosomal findings that include normal chromosomes (NN), abnormal chromosomes (AA), normal/abnormal chromosomes (N/A), hyperdiploid (greater than 50), hyperdiploid (47-50), hypodiploid (45-36), hypodiploid (less than 36), pseudodiploid, normal number (46), translocations, deletions and markers. There were no patients with Philadelphia chromosome positive. No relation was found when known PF were compared with chromosomal findings. Those factors which influenced relapse-free survival included: (a) age 24 months to 120 months vs greater than 120 months (b) hemoglobin less than 12 gm vs greater than 12 gm (c) initial WBC less than 20,000 vs greater than 100,000 and (d) failure to achieve bone marrow remission at day 28. No differences in relapse-free survival were found among the different chromosome groups. (no Refs)

7. CHROMOSOMES AND CAUSATION OF HUMAN CANCER AND LEUKEMIA. XLVII. SEVERE HYPODIPLOIDY AND CHROMOSOME CONGLOMERATIONS IN ALL.

Sandberg AA, Wake N, Kohno S
Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Cancer Genet Cytogenet; 5(4):293-307 1982

A case of acute lymphoblastic leukemia (ALL) of the L1 type with severe hypodiploidy in the marrow cells (modal chromosome number, 36) is described. In addition, most of the metaphases contained chromosome conglomerations which consisted of varying numbers of chromosomes and appeared similar to conglomerations previously observed by us in a case of chronic myelocytic leukemia (CML) in the blastic phase (BP), where some cells contained less than 20 chromosomes. The karyotype of the ALL cells of our case was similar to those of published near-haploid ALL cases, possibly indicative of a common pathway of cytogenetic evolution. (Author abstract) (15 Refs)

8. DEL(16)(Q21 OR 22) AND MARROW EOSINOPHILIA IN ACUTE NON-LYMPHOBLASTIC LEUKEMIA (ANLL): A NEW CYTOGENETIC--CLINICAL ASSOCIATION (MEETING ABSTRACT)

Bloomfield CD, Arthur DC
University of Minnesota, Minneapolis, MN, 55455
Proc Am Soc Clin Oncol; 1:C-742 1982

Certain chromosome abnormalities in ANLL have been associated with characteristic clinical features (eg t (15;17), APL (acute premyelocytic leukemia) and disseminated intravascular coagulation). We now report a new cytogenetic-clinical association: a partial deletion of chromosome 16 and bone marrow (BM) eosinophilia. G-banded BM metaphase chromosomes were studied pretreatment in 43 consecutive ANLL patients (pts). A clonal chromosome abnormality was seen in 26 of the 41 pts in whom there was adequate material for study. Four (10%) had as their only abnormality a partial deletion of the long arm of one chromosome 16. Twenty-four to 67% of metaphases were abnormal. In 2 pts the break point was q 22; in 2 it appeared to be q 21 but the material was not optimal. For most clinical and hematologic features the 4 pts differed. The pts ranged in age from 1 to 79 years; 3 were male. By the FAB classification, 2 were M2 and 2 M4. Initial leukocyte counts ranged from 2.8 to 54.2 x 10(9)/l. The only unifying clinical feature found was BM eosinophilia. BM eosinophils (eos) were 8.3%, 9.0%, 18.2% and 53.8%. All the other 37 ANLL pts had less than 4.2% eos; 34 had less than 2%. One pt refused therapy and died at 1 mo; one died a toxic death on day 14 of therapy. Two pts obtained complete remission (CR) and remain in CR at 10 and 19 mos respectively. Interestingly, BM eosinophilia has been found at M D Anderson Hospital to predict long survival. Although study of more cases is required, our data suggest that del(16)(q 21 or 22) in ANLL results in BM eosinophilia. (no Refs)

9. RESPONSE TO 5-AZACYTIDINE IN PATIENTS WITH REFRACTORY ACUTE NONLYMPHOCYTIC LEUKEMIA AND ASSOCIATION WITH CHROMOSOME FINDINGS.

Larson RA, Sweet DL, Golomb HM, Testa JR, Rowley JD
Box 420, 950 E. 59th St., Chicago, IL, 60637
Cancer; 49(11):2222-2225 1982

Fifteen patients with acute nonlymphocytic leukemia (ANLL) who either had a relapse after a previous complete remission (nine patients) or progressive disease after initial induction attempts with combination chemotherapy (six patients) were treated with 5-azacytidine. Five patients (33%) achieved a complete remission (CR); of these, three had a relapse and died 30, 35, and 38 wk after 5-azacytidine therapy was begun. Two patients are still alive at 39 and 138 wk. Chromosomes were analyzed at the time of diagnosis; ten patients had a normal karyotype and five had an abnormal karyotype. Three of the five CR patients had an abnormal karyotype initially. Two of these individuals had a translocation of chromosomal material from a No 8 chromosome to a No 21 chromosome, t(8;21); this particular translocation has been associated with a better prognosis than have other types of chromosomal abnormalities in patients with ANLL. Even when abnormal chromosomes are present, 5-azacytidine can induce complete remission in patients with previously treated ANLL. (Author abstract) (11 Refs)

10. A COLLABORATIVE STUDY OF THE RELATIONSHIP OF THE MORPHOLOGICAL TYPE OF ACUTE NONLYMPHOCYTIC LEUKEMIA WITH PATIENT AGE AND KARYOTYPE.

Rowley JD, Alimena G, Garson OM, Hagemeijer A, Mitelman F, Prigogina EL
Box 420, 950 East 59th St., Chicago, IL, 60637
Blood; 59(5):1013-1022 1982

Data on the chromosome analysis of leukemic cells from consecutive patients with nonlymphocytic leukemia from six independent laboratories in the United States, Europe, and Australia were combined. The karyotypic pattern determined with banding was correlated with the patient's age and the morphological type of leukemia according to the FAB classification. Of the 503 patients in the combined study, 260 had acute myeloblastic leukemia (AML, M1 and M2), 142 had acute myelomonocytic leukemia (AMMoL, M4), 43 had acute monocytic leukemia (AMoL, M5), 30 had erythroleukemia (EL, M6), and 28 had acute promyelocytic leukemia (APL, M3). The percentage of patients with an abnormal karyotype was higher in EL (63%) and AML (59%) than in AMMoL (40%) and AMoL (42%). Loss of no. 5 and/or no. 7 occurred in 30% of all EL patients, in 19% of all AML patients, and in only 7% of AMMoL, in 5% of AMol, and in 4% of APL patients. These observations are significant because patients with ANLL secondary to aggressive therapy for a primary malignant disease tend to have AML or EL, and the majority have-5 and/or-7. These same morphological types of leukemia and the same abnormalities,-5 and/or-7, are also increased in patients with ANLL de novo who have a history of occupational exposure to potentially mutagenic substances. In the future, the type of leukemia and the particular karyotypic pattern may be useful in identifying a subset of patients with ANLL de novo whose leukemia may be mutagen-induced. (35 Refs)

11. PROGNOSTIC SIGNIFICANCE OF POSTTRANSFUSION HEPATITIS AND CHROMOSOMAL ABNORMALITIES IN ADULT ACUTE NONLYMPHOCYTIC LEUKEMIA.

Wong KK, Golomb HM, Rowley J, Baker AL, Testa J, Vardiman J

(c/o Golomb) Dept. Medicine, Univ. Chicago Hosp. and Clinics, Box 420, 950 East 56th St., Chicago, IL, 60637

Cancer Genet Cytogenet; 5(4):281-292 1982

In a retrospective analysis, we studied the effects of posttransfusion hepatitis (non-A, non-B) and chromosomal abnormalities upon the overall survival times of adult patients with acute nonlymphocytic leukemia (ANLL). Seventy-two patients treated at the University of Chicago from 970 to 981 were evaluable. The complete remission (CR) rate for the entire group of patients was 33%, and the median survival was 246 days. Twenty-eight patients (39%) developed hepatitis, and 42 (61%) did not. The CR rate of the patients with hepatitis was 54%, and the median survival of this group was 615 days. In comparison, the CR rate for those who did not develop hepatitis was 20%, and their median survival was 136 days (p less than 0.0001). The groups were comparable in terms of race, sex, initial hematologic parameters, chromosomal abnormalities, dates of treatment, chemotherapy treatment programs, and French-American-British (FAB) subtype, but the median age of the patients who did not develop hepatitis was higher than that of the others. Patients who had normal karyotypes and who developed hepatitis had the best overall prognosis (median survival of 738 days). Patients with abnormal karyotypes who failed to develop hepatitis had the shortest survival times (median, 124 days). The group of patients who had the longest survival (median, 1,130 days) included those over 40 yr old, with posttransfusion hepatitis, and with normal karyotypes. The development of posttransfusion hepatitis and the presence of chromosomal abnormalities appear to be important, but opposite, indicators of overall prognosis for patients with ANLL. (Author abstract) (19 Refs)

12. SEZARY'S SYNDROME.

Betti R, Marchegiani G, Gagliardi P

Divisione di Medicina Generale, Ospedale Zonale, Fabriano (Ancona), Italy

Minerva Med; 73(15):977-982 1982

Sezary's syndrome (SS) and its clinical aspects, diagnosis, prognosis, and treatment were discussed. A 72-yr-old man had for more 1 yr red, squamous cutaneous lesions on the whole body. Hepatosplenomegaly was observed and peripheral blood smear showed 36% of abnormal cells with big and small characteristic Sezary's cells. The increase in immunoglobulins (Ig) was due mostly to IgG and IgA. The karyotype study demonstrated 80% of normal chromosomes 46 (XY), and 20% of 92 (XXYY) and 184 (XXXYYY). The patients was treated with chlorambucil (10 mg/day). Bronchopulmonary infection developed and the patient died. (23 Refs) (In ITA)

13. CYTOGENETIC ABERRATIONS IN BLADDER CARCINOMA (MEETING ABSTRACT)

Roy JB, Dagg C, Bottomley RH

No affiliation given

77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Predicting the natural history of an early bladder tumor in any given patient poses a vexing problem. This is due to the fact that 70% of initial tumors recur and approximately 20% of them will eventually become upgraded, invasive and/or metastasize. Presently the routine histopathologic evaluation of resected tumors is of little value in differentiating tumors of low biologic potential from those that will ultimately prove fatal. The specific objective of our work is to evaluate the role of chromosomal aberrations in vesical cancer as a means of prognosticating the malignant behavior of those tumors. Specimens from 30 patients with transitional cell carcinoma were obtained and separated into 2 parts. One part was sent for routine histological exam and the other for chromosomal analysis. Chromosomal preparations were obtained by mincing the tissue in a special medium. The cell suspension was incubated with Colcemid followed by cell wall lysis with hypotonic KCL. After staining with Giemsa, metaphase spreads were counted and karyotypes were prepared. The histologic grade and stage of these 30 patients were correlated with their chromosomal analysis. The result showed that all 17 patients with low grade/stage had diploid or near diploid modal numbers with narrow distribution. On the other hand the 13 patients with high grade/stage tumors displayed aneuploidy with hyperdiploid modes and occasionally presence of marker chromosomes. (no Refs)

14. SEMINOMA AND EPIDIDYMAL CYSTS IN A YOUNG MAN WITH KNOWN DIETHYLSTILBESTEROL EXPOSURE IN UTERO (MEETING ABSTRACT)

Conley GR, Sant GR, Mitcheson HD

No affiliation given

77th Annual Meeting of the American Urological Association, Inc., may 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

A high incidence of male genital tract abnormalities occurs in males exposed to diethylstilbestrol (DES) in utero. Although female exposure to DES in utero has been linked to the development of adenosis and clear cell adenocarcinoma of the vagina, until now there has been no association between DES exposure and the development of male genital tract neoplasms. We report a seminoma developing together with ipsilateral epididymal cysts in a 26-year-old man with known DES exposure. His mother had taken DES antenatally from the first to the third trimester in amounts of up to 105 mg/day. Chromosome and sex chromatin analysis were normal and tumor markers were negative. Both testes were fully descended and the left was huge. Orchiectomy showed anaplastic seminoma and 2 epididymal cysts lined by columnar cells without apparent secretory cells and spermatozoa absent from the contained fluid. These appearances have been described for epididymal cysts of DES exposed males. In view of the known carcinogenic potential of DES in females exposed in utero, it is likely a similar potential exists in males. DES causes a high incidence of undescended and/or hypoplastic testes in humans and in experimental animals and these testes are known to be at increased risk for the development of seminoma. There may well be a causal relationship between DES exposure and development of seminoma. Although the DES-type epididymal cysts and seminoma may be coincidental in our patient, it gives rise to speculation as to the role of DES in testicular carcinogenesis. (no Refs)

DNA CONTENT AND PLOIDY CHANGES ASSOCIATED WITH CANCER

15. CHARACTERIZATION OF ABNORMALITIES IN DNA CONTENT OF HUMAN SOLID TUMORS (MEETING ABSTRACT)

Frankfurt OS, Slocum HK, Greco WR, Rustum YM
Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, NY, 14263
Proc Am Soc Clin Oncol; 1:C-25 1982

DNA ploidy index was estimated by flow cytometry in surgical samples of 242 human solid tumors. Cell suspensions were obtained by mechanical disaggregation and stained by DNA fluorochrome 4'-6-diamidino-2-phenylindole (DAPI) without fixation in the presence of detergent. Blood leukocytes were used as a diploid standard. In 74 tumors (31%) only diploid cells were observed (DNA index 1.0). In 160 tumors one aneuploid clone was found and only 8 tumors (6 colon and 2 lung) were characterized by the presence of two aneuploid clones. Two tumors had hypodiploid DNA content. Number of tumors with aneuploid cells in relation to total number of tumors investigated was: 46/60 lung cancer (primary and metastatic), 19/27 colorectal carcinoma, 18/25 breast carcinoma, 13/21 ovarian carcinoma, 18/24 renal carcinoma, 8/14 bladder carcinoma, 4/8 prostate carcinoma, 27/37 melanoma and 15/26 sarcoma. There was continuous distribution of DNA index from 1.08 to 2.9 with apparent clusters around 1.24, 1.65, 1.96 and 2.30. The existence of clustering was supported by a one-dimensional cluster analysis using the technique of Fisher. The largest group of aneuploid tumors (54%) had a median DNA value of 1.65 and ranged from 1.45 to 1.81. DNA ploidy indexes measured in the same tumor using DNA fluorochromes with different mechanisms of binding (DAPI or propidium iodide) were highly correlated (0.97). Values of DNA-index of tumors studied may be divided arbitrarily in 5 main groups: diploid, hyperdiploid, hypertriploid, tetraploid and hypertraploid. (1 Ref)

16. THE SIGNIFICANCE OF PLOIDY AND PROLIFERATION IN THE CLINICAL AND BIOLOGICAL EVALUATION OF BLADDER TUMORS: A STUDY OF 100 UNTREATED CASES.

Tribukait B, Gustafson H, Esposti PL
Dept. Medical Radiobiology, Karolinska Institutet, S-104 01, Stockholm, Sweden
Br J Urol; 54(2):130-135 1982

Cell material from 100 cases of newly diagnosed bladder tumors was studied with rapid flow cytofluorometric DNA analysis. The degree of ploidy and the percentage of cells in the S-phase characterizing the proliferation pattern of the tumors were determined from DNA histograms. The results were related to the tumor categories and to the histopathological grading of the tumors. Approximately 40% of T1 tumors showed aneuploid DNA patterns, while in the other categories aneuploidy was found in almost all cases. With few exceptions, tumors of Grade 1 were found to be diploid and tumors of Grade 3 aneuploid. In tumors of Grade 2, two-thirds were diploid and one-third aneuploid. In the group of aneuploid tumors the tetraploid cases exhibited the least malignant characteristics as judged by histological grades and tumor categories. The aneuploid non-tetraploid tumors increased in malignancy the more they deviated from tetraploidy. This might be explained by our observations of a positive correlation between the degree of ploidy and the degree of proliferation. The proliferation increased from 10% in tetraploid tumors to 20% in triploid and pentaploid tumors. (Author abstract) (14 Refs)

17. INDUCTION OF IN VITRO PROLIFERATION AND MATURATION OF HUMAN ANEUPLOID MYELOGENOUS LEUKEMIC CELLS.

Chiao JW, Andreeff M, Freitag WB, Arlin Z
Sloan-Kettering Inst. Cancer Res., New York, NY, 10021
J Exp Med; 155(5):1357-1369 1982

Terminal maturation of aneuploid leukemic cells from patients with acute myelogenous leukemia was induced by supplementation of media with lymphocyte-conditioned medium (CM). Cells in culture suspensions underwent changes in morphology, and some cell aggregates were detected. As the proportion of monocyte- and macrophage-like cells increased with time, the proportion of immature cells decreased. Flow cytometric measurement of cells during the maturation-induction period showed an appearance of cell populations having lower cellular RNA content than populations not treated with conditioned medium. CM-induced maturation of leukemic cells to monocyte- and macrophage-like cells appears to be independent of DNA abnormality. In three patients studied, hyperdiploid DNA stem lines were found in all cells throughout the culture period. Macrophage-like cells with mature functional and marker features had the same aneuploid stem line as the undifferentiated cells, establishing the leukemic origin of the differentiated cells. Because of the higher rate of proliferation in the CM-supplemented cultures than in those lacking CM, interaction of CM with cells seems to have resulted in stimulation of some cells from the resting to the replicating phase. (22 Refs)

18. GROWTH OF HUMAN MALIGNANT MICROMEGAKARYOCYTES IN VITRO.

Juneja HS, Williams WC, Minguell JJ, Bessman JD, Weiss GB, Gardner FH
Hematology-Oncology MW 404, Univ. Texas Medical Branch, Galveston, TX, 77550
Exp Hematol; 10(4):404-412 1982

Mononuclear cells from the peripheral blood of a patient with megakaryoblastic transformation of Philadelphia chromosome-positive chronic myelogenous leukemia were cultured. Morphological and cytochemical studies and cell ploidy determinations were done daily for 4 days. PAS staining of the cells increased progressively during culture. Ultrastructural study of circulating and cultured cells revealed demarcation membranes and alpha granules indicating the cells were micromegakaryocytes. Deoxyribonucleic acid synthesis, determined by 3H-thymidine uptake, peaked at 72 hr. The DNA content of cultured cells was diploid at all times. All 15 metaphases analyzed at 72 hr were Ph(1)-positive. Malignant (Ph(1)-positive) megakaryoblasts and micromegakaryocytes grown successfully were capable of partial cytoplasmic maturation as demonstrated by glycogen deposition and increase in subcellular organelles, while endoreduplication was impaired. Malignant megakaryoblasts and micromegakaryocytes can be grown successfully in short term liquid culture and have more complete maturation in vitro than observed in vivo. (Author abstract) (19 Refs)

19. FLOW CYTOMETRIC AND HORMONE RECEPTOR ANALYSIS OF DUNNING R3327 RAT PROSTATE TUMORS (MEETING ABSTRACT)

Wolf RM, Morse MJ, Herr HW, Kleinert EL, Melamed MR, Whitmore WF
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Proc Am Assoc Cancer Res; 23:945 1982

Since its introduction in 1961, the Dunning R3327 rat prostate tumor model has developed several different tumor lines by hormonal manipulation and genetic drift. These tumor lines have been characterized by histologic, biologic, histochemical, immunologic and other parameters. Flow cytometric (FCM) analysis along with estrogen receptors (ER) and androgen receptors (AR) by dextran-coated charcoal assay were measured in 4 histologically and behaviorally different Dunning R3327 tumor lines. The R3327G rapidly growing, anaplastic, estrogen insensitive tumor contained 72% hyperdiploid (greater than 2c) cells with 58% of the cells being of an aneuploid stem line 3.3-3.7c by FCM. This tumor is strongly positive for AR and negative for ER. Three R3327H tumor lines were analyzed. The first is a well differentiated, hormone sensitive tumor with only 9% hyperdiploid cells without aneuploid stem line and is AR and ER positive. The moderately well differentiated tumors developed from the same R3327H tumor line. One is slow growing, 18% hyperdiploid, without aneuploid stem line, AR positive, and ER negative. The other is very slowly growing, 15% hyperdiploid, without aneuploid stem line, and weakly AR and ER positive. FCM, AR, and ER are objective parameters to characterize and monitor Dunning R3327 rat prostate tumors. (no Refs)

CHROMOSOMAL FRAGILITY AND GENETIC FACTORS PREDISPOSING TO HUMAN CANCER

20. GENETIC ANALYSIS OF FAMILIAL CANCERS (MEETING ABSTRACT)

White R, Barker D, Cavenee W, Skolnick M
Department of Cellular, Viral, and Molecular Biology, University of Utah School of Medicine, Salt Lake City, UT
Thirty-fifth Annual Symposium on Fundamental Cancer Research, March 2-5, 1982, Houston, Texas. The University of Texas M. D. Anderson Hospital and Tumor Institute 38 pp., 1982.

Families that have a marked predisposition to the development of specific tumors, such as retinoblastoma, Wilms' tumor, and colon and breast cancer, may carry and segregate specific alleles at loci that interact with the biochemical pathway and thus lead to tumorigenesis. Genetic analysis of these individuals at both the organismal and cellular levels will provide the basis for a molecular genetic approach to the etiology of such tumors. The necessity of knowing the genotype of both individuals and their tumors can be met by genetic markers based on DNA sequence polymorphism. Markers defining arbitrary loci can be used in familial studies to confirm the genetic basis of observed familial clustering and to examine genetic events in tumors. DNA segments containing suspected oncogenes (for example, the human equivalents of the genes defined in animal cells transformed by retroviruses or in cells transformed with DNA isolated from tumors) can be used to develop polymorphic restriction fragment markers and, in turn, to determine the role of such oncogenes in the primary etiology of familial tumors. We will report our progress in using these approaches to study retinoblastoma and colon cancers. (no Refs)

21. FOLLOW UP OF FANCONI'S ANEMIA (FA) HIGH FREQUENCY OF ACUTE LEUKEMIA (MEETING ABSTRACT)

Schaison G, Leverger G, Yildiz I, Berger R, Bernheim A, Gluckman E
Hospital St Louis Paris, 75010 Paris, France
Proc Am Soc Clin Oncol; 1:C-529 1982

FA is a disease with recessive mode of inheritance characterized by an association of congenital malformations and bone marrow failure. A high rate of chromosomes breakage is observed in mitose from blood cell cultures but the karyotypes are otherwise normal. Forty-four cases of FA were treated in the same department between 1962 and 1976. There were 27 boys and 17 girls. Most of the patients were treated with androgens +/- corticosteroids. Nine patients died from acute granulocytic leukemia (myeloblastic or erythroleukemia). Bone marrow blasts were over 25%. Four patients have cytogenetic examinations and a clonal abnormality was present in 3. Chemotherapy was unsuccessful. Five other patients have a leukemic or a preleukemic state instead of a non blastic bone marrow: 4 patients have a clonal state and 2 of them died of aplasia; 2 are alive. A fifth patient died of hemorrhage with a large hepato-splenomegaly. Among the 30 patients, 12 are alive and 18 died, seven cerebral hemorrhages, 3 hepatic failure, 1 cardiac failure, 1 pancrealitis, 2 septicemias, and 4 GVH (graft vs host) after bone marrow graft. One patient grafted 4 years ago is alive in complete chimerism without any treatment. In our patients the rate of a leukemic or preleukemic state reached 30%. In 200 patients with acquired aplastic anemia, there is no one case of leukemia. We didn't find any case of leukemia in the parents or the sibship. (no Refs)

22. IN VITRO CHARACTERIZATION OF GARDNER SYNDROME, FAMILIAL POLYPOSIS COLI, HEREDITARY DISCRETE COLORECTAL ADENOMAS, AND COLORECTAL CARCINOMA (MEETING ABSTRACT)

Gardner E, Burt R, Edward S, Neff L
Utah State University, Salt Lake City, UT
Am J Hum Gen; 33(6):63A 1982

Samples from large kindreds with Gardner syndrome (K 109), familial polyposis coli (K 267, K 268, and K 269), hereditary discrete colorectal adenomas (K 133), and individuals with invasive or recurrent colorectal carcinoma have been obtained. The samples include skin biopsies from the upper arm for fibroblast culture, adenoma biopsies from upper and lower astrointestinal tract with flexible endoscopes for fibroblast culture, and peripheral blood for mutagen challenge and sister chromatid exchange. Fibroblast cultures have been characterized for saturation density and growth on different levels of fetal calf serum. Fibroblast chromosomes have been G-banded, karyotyped, and characterized for structural and numerical instability, polymorphism in chromosome number 2, mutagen challenge, and sister chromatid exchange. More than 100 fibroblast lines have been frozen for future use and futher comparsions. Lymphocyte chromosomes have been G-banded, mutagen challenged, and scored for sister chromatid exchange. With these tests, different polyploid and cancerous conditions are distinguished in vitro on the basis of cell culture and chromosome criteria. Random chromosome instability and chromosome number 2 heteromorphism data will distinguish Gardner syndrome and familial-polyposis coli patients from those with hereditary discrete polyps and normal controls. Response of sister chromatid exchange with mitomycin-C mutagen challenge will distinguish Gardner syndrome, invasive colon cancer, recurrent colon cancer, hereditary discrete polyp patients, and controls for each other. (no Refs)

23. A FAMILIAL AGGREGATION OF PANCREATIC CANCER: AN IN VITRO STUDY.

Danes BS, Lynch HT
Lab. Cell Biology (D-209), Dept. Medicine, Cornell Medical Coll., 1300 York Ave., New York, NY, 10021
JAMA; 247(20):2798-2802 1982

The incidence of pancreatic cancer has been increasing steadily in the United States and other industrialized nations. Its obscure etiology and difficult early diagnosis tend to hobble effective control programs. Innovative methods, such as biomarkers, might provide clues to its inevitable occurrence in high-risk individuals. We studied a family in which four individuals manifested pancreatic cancer verified through two generations. Cell cultures from split-thickness skin biopsy specimens were obtained from 24 members from three generations (17 bloodline relatives, 7 family members by marriage) as well as 10 nonfamily normal subjects, none with a family history of solid tumors. One of the constant features of human monolayer dermal cultures has been diploidy. Hyperdiploidy, other than tetraploidy, has been rarely observed in cultures from normal subjects without a family history of solid tumors. We observed increased in vitro hyperdiploidy in 8 of 17 family members studied. (Author abstract) (33 Refs)

24. PAPILLARY RENAL CELL CARCINOMA IN TWO BROTHERS ASSOCIATED WITH TRANSLOCATION OF CHROMOSOMES 13 AND 14 (MEETING ABSTRACT)

Sanchez M, Bahng K, Ibrahim I
Englewood Hospital, Englewood, NJ
71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

Two brothers, native of Colombia, ages 40 and 42 presented simultaneously with renal cell carcinoma showing very prominent papillary features. Chromosome analysis of peripheral blood lymphocytes revealed 45XY (T13; 14) in both patients. An expedition to Colombia collected 49 blood samples of sibling and next generation family members, ranging from 14 to 54 years of age. Nine were affected by the same translocation. They are now being followed. The association of clear cell carcinomas of the kidney with T(3:8) (p21; q24) has been described. Familial renal cell carcinomas may be associated with a variety of chromosomal abnormalities with specific multiple histologic patterns. The analysis of chromosomes in unusually young patients with renal tumors may lead to early diagnosis and treatment of familial renal cell carcinoma with chromosomal abnormalities. (no Refs)

25. FAMILIAL GLIOMAS: REPORT OF FOUR FAMILIES, WITH CHROMOSOME STUDIES.

Chadduck WM, Netsky MG, Salcman M, Bigner DD
Post Office Drawer 4666, Martinsville, VA, 24115
Neurosurgery; 10(4):445-449 1982

Eight case reports of glioma in four families are presented along with computed tomography scans and histologic results. In addition to chromosome analysis, cases were reviewed with respect to common environmental factors such as diet, atmospheric toxins or exposure to viral infections. Low grade, 'mirror' tumors were found in two brothers of one family and multiple CNS abnormalities were found in another family which suggest an inclusive genetic abnormality of the nervous system. Karyotyping studies were done on peripheral blood samples; normal chromosome numbers and patterns were found in all cases. Additional studies on chromosomal analysis of cultured tumor cells or a comparison of blood and tumor cells might yield additional information. Previous studies indicated a genetic factor in neurological disorders; one investigation disclosed seven cases of glioma among 5,262 relatives of 100 patients with glioma, while none were found among controls. The authors suggest formation of a tumor registry to report cases of familial gliomas. (14 Refs)

26. TETRASOMY 21 IN AN INFANT WITH DOWN SYNDROME AND CONGENITAL LEUKEMIA.

Jabs EW, Stamberg J, Leonard CO
Dept. Pediatrics, CMSC 1004, Johns Hopkins Hosp., Baltimore, MD, 21205
Am J Med Genet; 12(1):91-95 1982

A case of tetrasomy 21 is described in a white infant born at 32 wk with Down syndrome and congenital monocytic leukemia. Fifty cells from a peripheral blood sample obtained at 3 days of age using standard culturing techniques, including phytohemagglutinin stimulation, were studied by quinacrine fluorescent and reverse banding techniques. All cells had 48 chromosomes with four number 21 chromosomes. (29 Refs)

27. GENETIC STUDIES ON HYDATIDIFORM MOLES. I. THE ORIGIN OF PARTIAL MOLES.

Lawler SD, Fisher RA, Pickthall VJ, Povey S, Evans MW
Royal Marsden Hosp., Fulham Road, London, SW3 6JJ, England
Cancer Genet Cytogenet; 5(4):309-320 1982

A study was designed to investigate the genetic origin of hydatidiform moles. Fifty-nine specimens were obtained and, on a histological basis, separated into two entities: complete and partial. The study of the genetic origin of the 15 partial moles, using cytogenetic and biochemical markers, is described. All the partial moles examined cytogenetically were triploid. One had 71 chromosomes. The sex chromosome complements of seven cases were six XXY and one XXX. Origin by dispermy was possible in seven cases and was proven in four. With the use of biochemical markers a maternal contribution was identified in three cases, and the isoenzyme pattern suggested a trisomic state or at least one locus in four cases. The mechanism of origin of partial moles was compared with spontaneously aborted and liveborn triploids. All the patients were followed up for at least 9 mo, and none required treatment for persistent trophoblastic activity. (Author abstract) (39 Refs)

CHROMOSOMES OF HUMAN CELL LINES AND TUMORS IN VITRO

28. CYTOGENETIC AND PHENOTYPE CHARACTERISTICS OF 6-THIOGUANINE (6-TG)-RESISTANT CULTURED HUMAN PROMYELOCYTIC LEUKEMIA (HL-60) CELLS (MEETING ABSTRACT)

Ferrari AC, Testa JR, Gallagher RE
National Cancer Institute, Baltimore Cancer Research Program, Baltimore, MD
Am J Hum Gen; 33(6):62A 1982

Cytogenetic studies of HL60 cells resistant to increasing concentrations of 6-TG (0.5, 5, 20 and 50 ug/ml) were performed in order to determine any association between chromosome pattern and two known responses to 6-TG: cytotoxicity and terminal differentiation. Cytogenetic preparations of control and resistant cells were stained sequentially with Giemsa, ethidium bromide, and quinacrine mustard. Control cells had a modal chromosome number of 45; less than 1% had double minutes (dm). For cells resistant to 0.5, 5, or 20 ug/ml 6-TG, the modal number was 45 with few (less than 11%) cells having greater than 46 chromosomes; dm were found in 42-67% of the cells. The number of dm per cell ranged from 1-5 at 0.5 ug/ml and at 5 ug/ml and from 6-10 at 20 ug/ml 6-TG. Forty-six per cent of the cells resistant to 50 ug/ml 6-TG had greater than 46 chromosomes (38% with counts of 47-49). The shift in chromosome number at 50 ug/ml 6-TG was associated with a marked decrease in the percentage of cells with dm (5.7%). Thus far, we have been unable to find any prominent homogeneously staining regions (HSR) in the cells resistant to 50 ug/ml 6-TG. Compared to control cells, the resistant cells had markedly reduced or absent hypoxanthine-guanine phosphoribosyltransferase (HGPRT) activity as determined by pulse labelling with 3H-hypoxanthine and HGPRT enzyme assays. The ability of 6-TG or hypoxanthine to induce terminal differentiation was not affected up to 20 ug/ml of drug resistance. We conclude: 1) cytotoxic resistance is due to the loss of HGPRT and is associated with acquisition of dm, which, thus, do not contain the genes for active HGPRT; 2) terminal differentiation induced by purines is related neither to cytoxicity nor to the dm; and 3) loss of dm in the 50 ug/ml 6-TG resistant cells seems not to be associated with the development of HSR as in other systems, although the possible presence of amplified genes requires further analysis. (no Refs)

29. IN VITRO CLONING OF HAIRY CELL LEUKEMIA (HCL) (MEETING ABSTRACT)

Hofmann V, Merchant R, Fehr J, Fruh U, Kiser A, Muller HJ, Martz G

Division of Oncology, University Hospital, 8091 Zurich, Switzerland

Proc Am Soc Clin Oncol; 1:C-530 1982

The present report describes the in vitro cloning of hairy cells (HCs) from spleen and/or peripheral blood of 9 HCL patients (pts). Ficoll-separated mononuclear cells (5-100% HCs) either unfractioned or after T-cell depletion with sheep red blood cells were plated at concentrations ranging from 0.1-1.6x10(6)/ml in alpha-MEM (minimum essential medium) containing methylcellulose (1.6%) and leukocyte-conditioned medium (0.2-0.8%) stimulated with phytohemagglutinin for 7 d. Growth was monitored daily: clusters (3-40 cells) became apparent after 48 hr and colonies (40-500 cells) between d 4 and 6. Colonies were round and compact. Up to 10% of cells in colonies incorporated 3H-thymidine when examined autoradiographically. Cytogenetics revealed numerous metaphases. All 9 HCL samples grew with cloning efficiencies of about 0.1%. Peripheral blood from 3 pts with CLL (chronic lymphocytic leukemia) and 2 with Sezary syndrome failed to grow in the same system. Several techniques were applied to prove origin of cells in colonies. Fifty-95% of cells in colonies displayed strong tartrate-resistant acid phosphatase activity. Ultrastructure analysis also confirmed their HCL characteristics. So far, marked cytogenetic abnormality has been found in 1/4 HCL. (no Refs)

30. ESTABLISHMENT AND CHARACTERIZATION OF A HUMAN RENAL CELL CARCINOMA CELL LINE IN VITRO AND IN NUDE MICE (MEETING ABSTRACT)

Lewis DA, Goldroeen MH, Sandberg AA, Beckley S, Pontes JE

No affiliation given

77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

A cell line was established from a primary renal cell carcinoma resected from a female patient who subsequently underwent successful specific active immunotherapy with autologous tumor cells and adjuvant for metastatic disease. A tumor specimen was subjected to a sequential enzymatic disaggregation by collagenase, hyaluronidase, pronase, and DNAse to obtain a single cell suspension. Cells suspended in RPMI-1640 plus 10% fetal bovine serum and placed in tissue culture flasks were adherent in 6-12 hours and grew as a monolayer to confluency. Monolayers were subcultured by exposure to 0.25% trypsin. After 5 passages in vitro, the cells were homogeneous and displayed a well defined globular shape with pseudopod-like structures. At the 23rd in vitro passage the cell line demonstrated hypertetraploidy with extra chromosomes in almost all groups. Deletion of the long arms of chromosomes 6 and 11 and an isochromosome of number 1 were observed. After 19 in vitro passages, 5x10(6) cells/mouse were injected subcutaneously into the backs of 12 male and 8 female randombred Swiss Nu/Nu mice. Tumors appeared in 7-10 days in 7/8 females and 1/12 males. This is consistent with the fact that the original tumor possessed estrogen receptors. The histology of the nude mouse tumors was consistent with the original diagnosis of a poorly to moderately differentiated renal cell carcinoma. (no Refs)

31. CHARACTERIZATION OF A HUMAN CELL LINE ORIGINATED FROM A RADIATED TRANSITION CELL CARCINOMA OF THE BLADDER (MEETING ABSTRACT)

Pontes JE, Sandberg AA, Morrison K, Pierce JM

No affiliation given

77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

A 66 year old white man underwent a salvage cystectomy for a previously radiated bladder neoplasm. Pathologically a Stage T3 N0 poorly differentiated transitional cell carcinoma with squamous elements was found. The tumor removed at the operating room was placed under sterile conditions on tissue culture media and taken to the laboratory. The tumor was cut into small pieces and placed on a T 24 flask (Falcon) with complete MEM (minimum essential medium) and 20% FCS (fetal calf serum). Monolayers were split by trypsinzation and this tumor has now been carried to the 73rd passage. Growth rate of this line was determined using a microculture method. The mean doubling time for the Gibb cell line based on 16 determinations is 23.4 hours +/-3.5 hours. Cells from the 6th, 18th and 23rd passage were injected subcutaneously in the nude mice. Tumors grew slowly and the centers became necrotic after the tumors reached over 1 cm in diameter. Histologically they were similar to the primary tumor. Chromosomal analysis on cell from the 23rd passage showed that most of the cells were pseudodiploid or hypoploid (ie 46 and 45 chromosomes respectively). The most common karyotype was: 46, X, -Y, +9, 14q-, 15q-,-18 and a marker chromosome. Evaluation of these cells by electron microscopy revealed characteristics of transformed epithelial cells such as the presence of microvilli

(SEM) and the presence of tonofibrils and desmosomes (TEM). (no Refs)

32. CYTOGENETIC AND BIOCHEMICAL CORRELATES OF MORPHOLOGICALLY DIVERGENT CELL TYPES HUMAN NEUROBLASTOMA CELL LINES (MEETING ABSTRACT)

Biedler JL, Meyers MB, Ross RA, Spengler BA
Sloan-Kettering Institute and Fordham University, New York, NY
Am J Hum Gen; 33(6):61A 1982

Human neuroblastoma lines established in culture often comprise two morphologically diverse types of cells: a small, weakly adherent neuroblast-like cell with neuritic processes (N-type) and a seemingly larger, flattened, substrate adherent cell (S-type) resembling normal epithelial or fibroblast cells. We have isolated sublines of each cell type from 5 different human lines (SK-N-SH, SK-N-BE (1), LA-N-1, SMS-KCN, and CHP-234) either by cloning or by selective culturing techniques. Presence of structurally rearranged marker chromosomes indicates a common cellular origin for the N-type and S-type cells of each set. The 2 cell types differ in many respects. Double-minute chromosomes (DMs), frequently found in human neuroblastoma cells, are more numerous and/or larger in the N-type cell compared to the substrate-adherent S-cell counterpart. Neurotransmitter-synthesizing enzyme activities are low or undetectable in the S-type as compared to the neuroblastic N cells. SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis) analysis of soluble proteins suggests a greater amount of presumptive actin in S cells. However, 2D gel analysis shows no increase in synthesis of actin in S-type cells; rather, these cells contain a family of at least 6 acidic proteins with similar isoelectric points but different molecular weights (ranging from 30-40 KD). These findings indicate that malignant neuronal cells in culture can display markedly different phenotypes that arise spontaneously. (no Refs)

33. CYTOGENETIC ANALYSIS OF SINGLE HEMOPOIETIC COLONIES IN LEUKEMIA CAN REVEAL DIFFERENT CELL POPULATIONS FROM THOSE IDENTIFIED IN DIRECT PREPARATIONS (MEETING ABSTRACT)

Dube ID, Kalousek D, Gupta C, Eaves C, Eaves A
B. C. Cancer Research Centre and University of British Columbia, Vancouver, British Columbia, Canada
Am J Hum Gen; 33(6):62A 1982

Cytogenetic analysis of bone marrow and circulating blast cells is routinely used to monitor cell population changes in patients with chromosomally marked hemopoietic disease. Recently we developed a method that allows the recognizeable progeny of individual hemopoietic progenitor cells to be analyzed cytogenetically in a routine fashion. This technique is now being applied to the investigation of patients with various types of leukemia. Ten cases have been studied to date. In 3 we have observed discrepancies between the cytogenetic findings obtained from the direct preparations and those from simultaneously cultured hemopoietic colonies. In one patient with untreated CML analysis of 31 marrow metaphases revealed only a 46, XX, Ph1 karyotype while 11 erythroid and 2 granulocyte colonies cultured at the same time from progenitors in the blood were all 46, XX. In another patient with untreated CML and myelofibrosis 25 metaphases were obtained from unstimulated blood and these revealed 2 cell lines (46, XX, Ph1 and 46, XX, Ph1 i(17q)) in equal proportions. In contrast 7 granulocyte/macrophage colonies and 5 erythroid colonies cultured from the same specimen were all 46, XX, Ph1. A similar observation was made in a patient in the acute phase of CML where the direct marrow revealed a 46, XX, Ph1/44, XX, +del(6q), 9q+,-17,-18,-19,-22, +mar mosaic while more than 100 hemopoietic colonies analyzed were all 46, XX Ph1. These findings demonstrate further the feasibility of performing cytogenetic analysis on single hemopoietic colonies. In addition they suggest that such studies may help in the investigation of mechanisms that regulate normal and abnormal cell proliferation in patients with leukemia. (no Refs)

34. CHEMOTHERAPY OF HUMAN BREAST CARCINOMA TRANSPLANTATION INTO NUDE MICE (MEETING ABSTRACT)

Benjamin I, Rana MW
St. Louis University Medical Center, St. Louis, MO, 63104
Fed Proc; 41(3):1477 1982

Human breast carcinoma in nude mice were produced by transplanting tissue from metastatic breast carcinoma in lung in a 44 year old white female. When tumors were about 1 cm in size the mice were divided into three groups. Group I received Adriamycin and Cisplatinum. Group II received the same combination of drugs with hyperthermia. Group III served as control. Although there was some regression of tumors in both Groups I and II, chemotherapy alone was as effective as combination therapy with hyperthermia. As estrogen receptor studies were negative on the transplanted tumors, treatment with antioestrogens were not done. Chromosome studies on the cultured tumor cells from control mice showed only mouse chromosomes. Our earlier experiments with human squamous cell carcinoma of cervix in nude mice had shown beneficial effect with hyperthermia in combination with chemotherapy. More studies are in progress using higher doses of chemotherapy with hyperthermia on animal models of Human breast carcinoma in nude mice. (no Refs)

35. PHENOTYPE OF HYBRIDS BETWEEN LYMPHOID CELLS AND RAT HEPATOMA CELLS.

Junker S
Inst. Human Genetics, Univ. Aarhus, DK-8000 Aarhus C, Denmark
Exp Cell Res; 139(1):51-61 1982

Subtetraploid rat hepatoma cells were fused with diploid or tetraploid lymphoid cells of various origins. All hybrid cells, analyzed 28 hr to 26 days after fusion, expressed basal and steroid-induced activities of the liver-specific enzyme tyrosine aminotransferase within the range given by the parental hepatoma cell line. Only the rat enzyme was produced in the hybrids. This was true, irrespective of the gene dosage of the lymphoid partner cell and of the presence of human X chromosomes. In contrast, the lymphoid phenotype, as monitored by production of kappa light chains specified by the diploid and tetraploid lymphoid partner cells, was totally suppressed within 72 hr after fusion. No difference in phenotypic expression was observed, whether the hybrid cells were grown as monolayer or as suspension cultures. (Author abstract) (41 Refs)

36. FUSION OF EBV TRANSFORMED B CELL LINES WITH MURINE MYELOMAS AS A VIABLE ALTERNATIVE FOR PRODUCTION OF HUMAN MONOCLONAL ANTIBODIES (MEETING ABSTRACT)

Kozbor D, Chang TH, Steplewski Z, Roder JC, Koprowski H
Department of Microbiology and Immunology, Queen's University, Kingston, Canada
Hybridoma; 1(2):200 1982

Peripheral blood B lymphocytes from donors immunized with tetanus toxoid (TT) were preselected for antigen (TT) binding cells followed by transformation with Epstein Barr virus (EBV) and cloning. A clone (B6) secreting the highest amount of monoclonal anti-TT was fused with a non-Ig secreting murine myeloma (P3x63Ag8 variant 653), selected in HAT medium containing 10-5M Oubain and cloned. Four clones selected for study were found to secrete 10-fold more monoclonal anti-TT antibody (1-2 ug/ml IgM kappa) during the six day culture period, than the parental line (B6). Human x mouse hybridoma clones required much less serum (1%) for growth and Ig production. Hybrids have been stable for 5 months and possess a full complement of murine chromosomes and a mean of 24 human chromosomes. The results show that hybridomas between EBV lines and murine myelomas offer advantages of (1) increased stablity; (2) increased antibody production; and (3) reduced serum requirement for growth in vitro. Since EBV is a known polyclonal activator, this technique suggests the possibility of expanding human B cells of rare antigen specificities prior to fusion. (1 Ref)

CHROMOSOMES OF ANIMAL CELL LINES AND TUMORS

37. MOUSE MYELOID LEUKEMIA AS AN EXPERIMENTAL MODEL FOR MONITORING PROGRESSION OF LEUKEMIA AND CHEMOTHERAPY (MEETING ABSTRACT)

Au WW, Otten JA, Luippold HE, Kennel SJ
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Proc Am Assoc Cancer Res; 23:874 1982

A transplantable leukemic cell line from x-ray induced mouse myeloid leukemia is used as a model for monitoring the progression of leukemia and chemotherapy. This particular cell line was a deleted chromosome number 2 which is characteristic of mouse myeloid leukemia. In addition, it contains a chromosome marker, an isochromosome number 8, with minimum loss of genetic material based on banding study. This marker is therefore the largest chromosome in the complement and is the only metacentric chromosome so that it can easily be identified even without banding analysis. Since the marker contains all the genetic material coded by chromosome 8, this marker is essential for survival even for leukemic cells after transplantation into host mice, the leukemic cells can be found in the bone marrow and the spleen. The leukemic cells can be unequivocally identified from co-existing normal cells therefore the progression of leukemia and susceptibility of leukemic cells from chemotherapeutic drugs can be monitored. (no Refs)

38. HIGH FREQUENCY OF IN VIVO SISTER CHROMATID EXCHANGES IN THE BONE MARROW CELLS OF MICE BEARING MAMMARY ADENOCARCINOMA DBRB.

Banerjee R, Goldfeder A, Mitra J
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Cancer Genet Cytogenet; 5(4):321-326 1982

Sister chromatid exchanges (SCEs) in vivo were evaluated in the bone marrow cells of mice bearing mammary adenocarcinoma dbrB of 0.5 and 1.0 cm3, respectively. It has been observed that the SCE frequency is significantly higher (p less than 0.001) in the bone marrow cells of tumor-bearing mice as compared to the bone marrow cells of non-tumor-bearing mice. SCE frequency in the bone marrow cells of mice with 1.0-cm3 tumors did not increase appreciably with tumor size as compared to that in the bone marrow cells of mice with 0.5-cm3 tumors. This indicates the presence of mammary carcinoma-induced somatic stress as noted in the genetic material of the bone marrow cells of the host. (Author abstract) (31 Refs)

39. T-CELL HYBRIDS. II. BH2 LINE-DERIVATION BY FUSION BETWEEN TWO (BW5147 X EL-4R) THYMOMA LINES.

Bubenik J, Perlmann P, Jonsdottir I, Kypenova H, Bubenikova D, Indrova M, Loudova M
Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 160 00 Prague 6, Czechoslovakia
Neoplasma; 29(1):3-7 1982

We have established the hybrid cell line BH2 derived from fusion between an AKR thymoma BW5147 and C57Bl thymoma EL-4R. The hybrid cells carry H-2 alleles from both parental lines and show a near-tetraploid modal number of chromosomes in contrast to the near-diploid stem-lines of both parental cell populations. (Author abstract) (11 Refs)

GENE MAPPING STUDIES

40. HUMAN TRANSFERRIN RECEPTOR: EXPRESSION OF THE RECEPTOR IS ASSIGNED TO CHROMOSOME 3.

Enns CA, Suomalainen HA, Gebhardt JE, Schroder J, Sussman HH
(c/o Sussman) Lab. Experimental Oncology, Dept. Pathology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Proc Natl Acad Sci USA; 79(10,part1):3241-3245 1982

Human chromosome 3 had been identified as responsible for expression of the transferrin receptor in mouse-human lymphocyte hybrids. The receptor was detected by immunoprecipitation with anti-human receptor antibody of 125I-labeled cells. This method also detected a similar 94,000-dalton protein in mouse cells. A radioimmunoassay developed for the human transferrin receptor measured 10% crossreactivity with the mouse protein. The two proteins were distinguished by NaDodSO4/polyacrylamide gel patterns of partial proteolytic digests of the immunoprecipitated proteins. Mouse-human hybrids were generated by fusing a mouse thymoma (BW5147) cell line to either concanavalin A- or pokeweed mitogen-activated human peripheral blood lymphocytes or a mouse myeloma (NS-1) to uncultured human peripheral blood lymphocytes. Each hybrid was karyotyped with respect to both mouse and human chromosomes. In every case, expression of the human transferrin receptor correlated only with human chromsome 3. (Author abstract) (32 Refs)

41. DBA/2HA MICE AS A MODEL OF AN X-LINKED IMMUNODEFICIENCY WHICH IS DEFECTIVE IN THE EXPRESSION OF TRF-ACCEPTOR SITES(S) ON B LYMPHOCYTES.

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Immunol Rev; 64:25-55 1982

An experimental system for analyzing functional properties of TRF-producing helper T cells and the genetic basis for the activation of B cells by TRF acceptor sites(s) using the DBA/2Ha mouse strain is described. Evidence that two distinct subpopulations of helper cells exist, one which collaborates with B cells with cognate interactions and the other which releases TRF and is genetically unrestricted in its interaction with B cells, is presented. The expression of TRF acceptor sites on the B cells is controlled by the X-chromosome-linked recessive genes. Two distinct subpopulations of B cells which differ in their activation requirements exist. (93 Refs)

MOLECULAR CYTOGENETICS

42. REGULATION OF DNA REPAIR IN HUMAN CELLS (MEETING ABSTRACT)

Sirover MA, Gupta PK
Temple University School of Medicine, Philadelphia, PA, 19140
Fed Proc; 41(3):686 1982

The regulation of excision repair genes was examined in normal human cells and in cells from cancer prone individuals. Synchronous cultures of WI-38 normal diploid fibroblasts and xeroderma pigmentosum (XP) cells were used to examine the cell cycle regulation of DNA repair. Cells were synchronized by serum depletion then stimulated to tranverse the cell cycle by the readdition of serum. DNA repair was assayed either as unscheduled DNA synthesis or as repair replication. In WI-38 cells, nucleotide excision repair was induced 2-4 fold reaching a maximum in cells exposed 14 hours after serum addition. Base excision repair was induced 2 fold reaching a maximum in cells exposed at 18 hours. DNA repair pathways were increased prior to the stimulation of DNA replication (22-24 hours). XP cells (groups A, C, and D) normally regulated base excision repair and DNA replication but failed to regulate nucleotide excision repair. Using a dose of 5 J/m2 no increase in nucleotide excision repair above basal levels was observed at any interval examined in the cell cycle. In the XP variant nucleotide excision repair was increased 2-4 fold as observed in WI-38 cells. However, the temporal sequence of induction was altered as the stimulation of the nucleotide excision repair pathway was delayed and occurred later in the cell cycle. These results suggest that normal human cells regulate excision repair genes in the cell cycle and that this regulation of gene expression is altered in XP cells. (no Refs)

43. EUKARYOTIC DNA REPAIR IS BLOCKED AT DIFFERENT STEPS BY INHIBITORS OF DNA TOPOISOMERASES AND OF DNA POLYMERASES ALPHA AND BETA.

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Biochim Biophys Acta; 697(1):6-13 1982

Inhibitors of (a) DNA topoisomerases (novobiocin and nalidixic acid) and of (b) eukaryotic DNA polymerses alpha (cytosine arabinoside) and beta (dideoxythymidine) blocked different steps of DNA repair, demonstrated by the effects of the inhibitors on the relaxation of supercoiled DNA nucleoids following treatment of human cell cultures with ultraviolet light (1-3 J/m2) or N-methyl-N-nitro-N-nitrosoguanine MNNG (5 or 20 uM) and the subsequent restoration of the supercoiled nucleoids during repair incubation. Changes in the supercoiling of nucleoid DNA were assayed by analysis of their sedimentation profiles in 15-30% neutral sucrose gradients. Inhibition of repair by novobiocin was partially reversible; upon its removal from the culture medium, the nucleoid DNA of repairing cells became relaxed. The DNA polymerse inhibitors allowed the initial relaxation of DNA after treatment of the cells with UV or MNNG but delayed the regeneration of the initial rapidly-sedimenting (supercoiled) nucleoid DNA for 2-4 hr. Dideoxythymidine (1 mM) was more effective than cytosine arabinoside (1 uM) in producing this delay, but neither inhibitor by itself blocked repair permanently. Incubation of ultraviolet-irradiated cells with 1 uM cytosine arabinoside plus 1 mM dideoxythymidine blocked the completion of repair for 24 hr, whereas incubation with 10 uM cytosine arabinoside or 5 mM dideoxythymidine produced only temporary repair delays of 2-4 hr. Thus, it is likely that the two DNA polymerase inhibitors act upon separate targets and that both targets are involved in repair. It is concluded from these and from previous studies that (1) the DNA repair-sensitive target of novobiocin and nalidixic acid in vivo is not a DNA polymerase, but, rather, a DNA topoisomerase; (2) this target affects an initial step of DNA repair leading to the relaxation of supercoiled DNA; (3) the DNA polymerization step of repair may involve both alpha- and beta-type DNA polymerases; and (4) in repair one type of DNA polymerase may substitute for another. (Author abstract) (33 Refs)

44. ROLE OF DNA REPAIR IN ETHYL METHANESULFONATE-INDUCED MUTAGENESIS IN SACCHAROMYCES CEREVISIAE.

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Carcinogenesis; 3(4):439-444 1982

Ethyl methanesulfonate (EMS)-induced reversion of two sites which revert preferentially by GC to AT transitions, cycl-131 and cycl-115, has been examined in radiation sensitive, rad, mutants of yeast belonging to the rad52 epistasis group. The rad50, rad51, rad52, rad54 and rad56 mutants showed reduced reversion of both tester sites when stationary phase diploid cells were treated with EMS. No correlation was found between EMS-induced reversion and EMS-induced homologous mitotic intragenic recombination. Survival of rad6 rad52 double mutants following EMS treatment indicates that there is one epistasis group for the repair of EMS-induced lethal damage in yeast. A model involving misrepair mutagenesis of specific lesions is proposed to account for the experimental results. (Author abstract) (39 Refs)

45. REPAIR OF DNA INTERSTRAND CROSSLINKS AFTER BUSULPHAN. A POSSIBLE MODE OF RESISTANCE.

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Cancer Chemother Pharmacol; 8(1):3-7 1982

The technique of alkaline elution was used to study the interaction between busulfan (BS) and the DNA of cells derived from the transplantable rodent Yoshida sarcoma. The findings were related to the in vitro cytotoxicity and chromosome aberrations (CHA) in the anaphase of cell lines resistant (YR) and sensitive (YS) to BS are discussed. The doses of BS producing 50% cell death were 7.5 and 54.5 ug/ml for YS and YR, respectively. BS (50 ug/ml) treatment in both cell lines caused a greater than two-fold depression in the mitotic index after 24 hr post-treatment incubation. A four-fold greater number of CHA could be observed in the YS than the YR line. Typical elution profiles in YS cells after a single 1-hr dose of BS (100 ug/ml) are presented. A small but reproducible proteinase-resistant retention was observed immediately after BS treatment, indicating the presence of DNA interstrand cross-links. As the dose of BS was increased, an increasing filter retention was observed, from which the number of cross-links per unit DNA could be assessed. The relationship between drug dose and the frequency of DNA interstrand cross-links is shown. A temporal study of DNA interstrand cross-linking after a single dose of BS (50 ug/ml; 1 hr) revealed a gradual increase in cross-linking over the first 4 hr, followed by a disappearance over 24 hr in the YR line. In the YS line, an increase in cross-linking over 4 hr and very little loss was observed 24 hr after drug removal. The time-course of cross-linking in both lines in terms of the relative retention is shown. (19 Refs)

46. MOLECULAR CLONING OF DOUBLE MINUTES FROM A HUMAN COLON CARCINOID CELL LINE (MEETING ABSTRACT)

Hubbell HR, Croce CM, Dolby TW
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Am J Hum Gen; 33(6):6A 1982

Double minutes (dms) are small, extrachromosomal fragments which naturally occur in a wide variety of human tumor cells. A subclone of the colon carcinoid line, COLO 320 DM CL 11, was used to obtain a chromosome subfraction enriched in dms. DNA isolated from this fraction was digested to completion with the restriction endonuclease Pst1 and inserted into the Pst1 site of pBR322. One clone containing a 4.0 kb insert, pDMC446, was selected for further study. Southern blot analysis of the parental line and two sister cell lines from the same biopsy, containing homogeneously staining regions (HSRs), showed amplification of the pDMC446 sequence with bands at 4.0 and 3.2 kb. The parental line had approximately 100 copies per cell of this sequence, or about 3 copies per dm. Thirteen other control and tumor lines, some containing dms or HSRs, showed background smearing, but no amplification. The smear was due to Alu family sequences found in the pDMC446 insert. Using a non-Alu containing fragment of pDMC446, a 4.3 kb band was seen with approximately equal intensity in the thirteen cell lines. These results indicate that: 1) dms are amplifications of normally occurring sequences, 2) dms and HSRs from the same biopsy contain the same sequences, 3) the organization of the DNA sequences in dms and HSRs is different from that in the normal genome, and 4) dms and HSRs from tumors of different histological types appear to contain different sequences. (no Refs)

47. THE SMALL CHROMATIN FRAGMENTS RELEASED BY MICROCOCCAL NUCLEASE FROM HEPATOMA TISSUE CULTURED CELL NUCLEI ARE STRONGLY ENRICHED IN CODING DNA SEQUENCES AND ARE RELATED TO AN ACTIVELY TRANSCRIBED SINGLE-STRANDED DNA FRACTION.

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Biochim Biophys Acta; 697(1):60-70 1982

It was shown with the use of specific probes that mild micrococcal nuclease digestion releases from chromatin actively-transcribed genes as small nucleosome oligomers. In the present work we demonstrate that most if not all of the active genes are accessible to the nuclease. It was found that the short released fragments are greatly enriched in transcribed DNA sequences, the most enriched being the dimers of nucleosomes since 35% of their DNA could be hybridized to cytoplasmic RNA. The results of cDNA-DNA hybridizations indicate that the monomers and dimers of nucleosomes contain most of the DNA sequences which encode poly(A+) RNAs, however larger released fragments include some transcribed sequences, while the nuclease-resistant chromatin is considerably impoverished in coding sites. These evidences and the finding that about 25% of the DNA from the dimers of nucleosomes are exclusively located in this class of fragments, tend to prove that the active chromatin regions are attacked in a non-random way by micrococcal nuclease. We have previously isolated, without using exogenous nuclease, an actively transcribed genomic fraction amounting to 1.5-2% of the total nuclear DNA, formed of single-stranded DNA. In the present study we show that all or nearly all the single-stranded DNA sequences could be reassociated with the DNA fragments present in the released monomers and dimers of nucleosomes. Our observations confirmed our previous finding that the greatest part of single-stranded DNA selectively originates from the coding strand of genomic DNA. (Author abstract) (34 Refs)

48. ON THE CHROMATIN STRUCTURE OF THE AMPLIFIED, TRANSCRIPTIONALLY ACTIVE GENE FOR DIHYDROFOLATE REDUCTASE IN MOUSE CELLS.

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Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139
J Biol Chem; 257(9):5274-5282 1982

The method for two-dimensional hybridization mapping of nucleosomes and was used to analyze chromatin structure of the gene for dihydrofolate reductase (DHF reductase; 5,6,7,8-tetrahydrofolate:NADP+ oxidoreductase) in L5178Y-R mouse cells. The DHF reductase gene in these cells is amplified about 350-fold as a result of selection for resistance to methotrexate. Dramatic overproduction of DHF reductase mRNA in L5178Y-R cells suggests that most of the DHF reductase genes in these cells are transcribed. We report that all major mononucleosomal species resolvable by two-dimensional fractionation are detected by both DHF reductase- and satellite DNA-specific hybridization probes. Although the DHF reductase and satellite hybridization patterns differ somewhat from each other and from the total mononucleosomal pattern, their overall similarity is very high. In particular, no large differences in the abundance of mononucleosomes containing high mobility group non-histone proteins (HMG) 14 and 17 are seen between the DHF reductase and satellite chromatin regions under a wide variety of conditions for chromatin isolation, digestion, and fractionation. Possible interpretations of the apparent lack of selectivity of HMG-chromatin interactions in this system are discussed. We also found that the amplified DHF reductase genes possess a wide range of nucleosomal repeat lengths close to that in the bulk chromatin. In contrast, the range of nucleosomal repeat lengths in the satellite chromatin is much narrower than in both DHF reductase and bulk chromatin. (Author abstract) (56 Refs)

49. ACUTE EFFECTS OF DIMETHYLNITROSAMINE (DMN) ON COMPOSITION AND SYNTHESIS OF RAT LIVER CHROMATIN PROTEINS (MEETING ABSTRACT)

Huang PH, Magee PN, Stewart BW
Temple University School of Medicine, Philadelphia, PA, 19140
Fed Proc; 41(3):687 1982

Administration to rats of the potent hepatocarcinogen DMN is followed by the methylation of hepatic nucleic acids and proteins. Consequent secondary structural changes in DNA may be detected by column chromatography on benzoylated DEAE (diethylaminoethyl)-cellulose. As part of the further investigation of nitrosamine-induced injury, short-term alterations in the composition of rat liver chromatin proteins have been analyzed. Administration of DMN (10 mg/kg) was associated with a proportional increase in the recovery of rat liver chromatin proteins for at least 48 hr after treatment and a biphasic increase in the incorporation of 14C-leucine into chromatin proteins. Upon further analysis of these proteins by one- and two-dimensional gel electrophoresis, changes in the histones and non-histone proteins electrophoretic mobility and staining intensity were detected. Incorporated 14C-leucine was distributed throughout all chromatin protein fractions analyzed 4 hr after DMN. During the period 24-48 hr, apparent preferential incorporation into histones occurred while at later times non-histone proteins were more highly radioactive. (no Refs)

50. FURTHER STUDIES ON THE CO-TRANSFORMATION OF DISTANT MARKERS FOLLOWING THE EXPOSURE OF DNA TO CARCINOGENS INCLUDING CARCINOGENIC METALS (MEETING ABSTRACT)

Kubinski H, Kubinski ZO
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Fed Proc; 41(3):685 1982

Exposure of Bacillus subtilis transforming DNA to chemical carcinogens produced a decrease in transforming activity of such DNA and a decrease in co-transformation of linked markers (tyr-trp). Under carefully controlled conditions an increase in co-transformation of distant (unlinked) markers (tyr-leu and trp-leu) was detected, indicating the formation of DNA-DNA complexes capable of penetrating into the interiors of the recipient cells. However, based on our studies of N-acetoxy-2-acetylaminofluorene - treated DNA, up to 80% of these complexes were eventually 'repaired', restoring the original chromosomal locations of these unlinked markers. Occasionally, the artificially linked pieces of DNA were inserted into adjacent loci in the recipients cell's chromosome. In separate studies, effects of various salts of chromium on the transforming DNA were investigated. An increased co-transformation of the unlinked markers was observed with Cr VI but not with Cr II or Cr III. The former, but not the latter are believed to produce tumors in humans. Thus, these observations support our earlier suggestion that only those mutational events which produce macromolecular complexes may be responsible for the malignant transformation in vivo. (no Refs)

51. MORPHOLOGICAL TRANSFORMATION, DNA STRAND SEPARATION, AND ANTINUCLEOSIDE IMMUNOREACTIVITY FOLLOWING EXPOSURE OF CELLS TO INTERCALATING DRUGS.

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Mol Pharmacol; 21(3):739-743 1982

Two structurally similar alkylating agents, the acridine derivatives proflavine and quinacrine were compared for their ability to induce morphological transformation and DNA strand separation in mouse 3T3 cells. The technique of antinucleoside immunofluorescence staining was used to detect the unwinding of DNA in nuclei of fixed cells. Treatment with proflavine resulted in higher transformation frequencies than were found with quinacrine. Results suggest that DNA strand separation is, or at least accompanies, an early step in cell transformation by intercalating drugs. (28 Refs)

52. EXPRESSION OF TRANSDUCED GENES IN MAMMALIAN CELLS (MEETING ABSTRACT)

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Thirty-fifth Annual Symposium on Fundamental Cancer Research, March 2-5, 1982, Houston, Texas. The University of Texas M. D. Anderson Hospital and Tumor Institute 38 pp., 1982.

Our laboratory has explored two approaches to achieving transduction-transformation of mammalian cells. One uses recombinants constructed in vitro from suitably modified cloned cDNAs or prokaryote and eukaryote-derived genomic segments and SV40 DNA from which segments encoding early and late viral functions have been excised. In this experimental design, the recombinant viral genomes must contain the origin of SV40 DNA replication and must not be larger than 5.3 kb in order to be propagated as mature virion genomes; moreover, since the recombinant genomes are defective, propagation can occur only with a helper virus to provide the missing gene product(s). A virtue of this approach is that amplification of the recombinant genomes ensures a high yield of the mRNAs and proteins expressed from the transduced genes. The second approach exploits a new group of transducing-transforming DNA vectors for the introduction and maintenance of new genes in a variety of mammalian cells. One prototype of this class of vectors, pSV2-neo, developed by Peter Southern and Bruce Howard, contains a DNA segment from the plasmid pBR322, in order to permit propagation of the recombinants in Escherichia coli, and a transcription unit comprising the SV40 early region promoter, the dominant selectable marker, Econeo, an intervening sequence, and a poly A site. Cells transformed with pSV2-neo (frequency, 10(-4) to 10(-5)) grow in media containing the inhibiting aminoglycoside G418. Unique restriction sites in pSV2-neo DNA permit the introduction of other, nonselectable genes into the same vector and, thereby, the cotransformation of cells for these otherwise nonselectable phenotypes. (no Refs)

53. ISOLATION AND CHARACTERIZATION OF C-MYC, A CELLULAR HOMOLOG OF THE ONCOGENE (V-MYC) OF AVIAN MYELOCYTOMATOSIS VIRUS STRAIN 29.

Vennstrom B, Sheiness D, Zabielski J, Bishop JM
Dept. Microbiology, Univ. Uppsala, Biomedical Center, Uppsala, Sweden
J Virol; 42(3):773-779 1982

The chicken genome contains nucleotide sequences homologous to the transforming genes (oncogenes) of a number of avian retroviruses. We have isolated chicken DNA (c-myc) that is homologous to the oncogene (v-myc) of the avian myelocytomatosis virus MC29 and have compared the structures of the cellular and viral genes. Results from restriction endonuclease mapping of c-myc and from analysis of heteroduplexes between the DNAs of the cellular and viral genes show that c-myc is homologous to 1,500 nucleotides in v-myc DNA. This homologous region is interrupted in c-myc by an intron-like sequence of 1,100 nucleotides which is absent from v-myc. Nuclear RNA from normal chicken cells contains at least five species of transcripts from c-myc ranging from 2.5 to 6.5 kilobases in length. By contrast, cytoplasm contains only the 2.5-kilobase c-myc RNA. These features of the c-myc gene and its nuclear transcripts are characteristic of normal cellular genes and suggest that the myc gene is of cellular rather than viral origin. The exons in c-myc may define two functional domains in the gene and may therefore facilitate the dissection of the different oncogenic potentials of the MC29 virus. (Author abstract) (28 Refs)

54. RESTRICTION MAPPING AND PHYSICAL CHARACTERIZATION OF THE COTTONTAIL RABBIT PAPILLOMAVIRUS GENOME IN TRANSPLANTABLE VX2 AND VX7 DOMESTIC RABBIT CARCINOMAS.

Favre M, Jibard N, Orth G
Unite 190 de l'Institut National de la Sante et de la Recherche Medicale, Unite des Papillomavirus, Institut Pasteur, Paris, France
Virology; 119(2):298-309 1982

The transplantable VX2 and VX7 carcinomas were analyzed for the presence, the nature, and the physical state of cottontail rabbit papillomavirus (CRPV) DNA sequences. Two CRPV DNA preparations, obtained from pooled cottontail rabbit papillomas, were found highly homogeneous as to their sensitivities to seven restriction endonucleases and were, therefore, considered as wild-type CRPV DNA. A cleavage map of the wild-type genome was constructed by locating 14 restriction sites. The carcinoma cells contained multiple copies of apparently whole viral genomes (42 and 444 genome equivalents per diploid VX2 and VX7 cell DNA contents, respectively), as determined by reassociation kinetic experiments and blot hybridization analyses of restricted VX2 and VX7 cell DNAs. Viral DNA molecules bearing a deletion of about 10% of the genome length, as well as minor sequence rearrangements, were also detected in VX7 carcinoma cells (about 25 copies per diploid cell DNA content). In both VX2 and VX7 cell DNAs, either unrestricted or treated with a no-cut endonuclease for the CRPV genome (PvuI), viral DNA sequences were present exclusively as slow-migrating species with similar electrophoretic mobilities. The conversion of these species into one-genome-unit-length linear DNA molecules, by a one-cut endonuclease for both wild-type and deleted DNA molecules (SmaI), shows that the viral sequences are not integrated in the cell genome. After cleavage of VX7 cell DNA by a no-cut endonuclease for deleted DNA molecules (EcoRI), the deleted molecules migrated with a mobility corresponding to form I and II DNA molecules. This suggests that the viral genomes may be present in carcinoma cells as free catenated DNA molecules. (Author abstract) (42 Refs)

55. HYBRID GAMMA2B-GAMMA2A GENES ACCOUNT FOR HYBRID IMMUNOGLOBULIN HEAVY CHAIN EXPRESSION IN SEVERAL MYELOMA VARIANTS (MEETING ABSTRACT)

Tilley SA, Eckhardt LA, Birshtein BK, Lang RB, Marcu KB
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Fed Proc; 41(3):832 1982

A number of variants expressing altered immunoglobulin heavy chains have been isolated from the MPC 11 (gamma 2b, kappa) cell line after mutagenesis. About 1/2 of these variants produce heavy chains bearing serological determinants of the gamma 2a subclass, and certain of these appear to be complete normal heavy chain class switch variants. Others produce hybrid gamma 2b-gamma 2a heavy chains, as confirmed for variant ICR 11.19.3 by protein sequencing. The ICR 11.19.3 heavy chain has its gamma 2b-gamma 2a junction within the CH2 domain in a region of sequence identity between gamma 2b and gamma 2a sequences. The heavy chains of three other MPC 11 variants appear highly similar but not identical to that of ICR 11.19.3 by peptide mapping, size, and charge. We present here Southern blot analysis of DNA from ICR 11.19.3 and like variants probed with JH region, gamma 2b- and gamma 2a-cDNA, and gamma 2b flanking region sequences. Comparison of these results to the MPC 11 DNA control shows rearrangement of the gamma 2b and gamma 2a genes to create a hybrid gamma 2b-gamma 2a gene in each of these variants. The hybrid genes are the same size as either a gamma 2b or gamma 2a gene alone, as expected, and are associated only with the expressed heavy chain chromosome of the MPC 11 cell line. The implications for aberrant heavy chain class switching and intradomain homologous recombination in a multi-gene family are discussed. (no Refs)

56. DNA REARRANGEMENTS IN MPC-11 IMMUNOGLOBULIN HEAVY CHAIN CLASS-SWITCH VARIANTS.

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Proc Natl Acad Sci USA; 79(9):3006-3010 1982

Immunoglobulin heavy chain class switching has been observed in vitro. In the IgG2b-producing MPC-11 mouse myeloma cell line, IgG2a-producing cells arise at a high frequency. In some cases, switch variants producing normal-sized (Mr 55,000) gamma2a heavy chains have arisen spontaneously from a mutagen-induced 'intermediate' (ICR 9.7.1) that produces an unusually large (Mr 75,000) heavy chain. Other switch variants have been isolated directly from the parent cell line. The expressed and unexpressed gamma2b genes of MPC-11 can be distinguished in restriction endonuclease digests of total genomic DNA so that DNA rearrangements detected in MPC-11 variants can be directly associated with one or the other of these two genes. We describe here DNA rearrangements occurring on the expressed heavy chain chromosome of several MPC-11 gamma2a switch variants and on the expressed chromosome of the ICR 9.7.1 intermediate. Our data indicate that all of these variants express the parental heavy chain variable region (VH) gene, supporting previous protein studies. We provide mapping data for the expressed gene of both ICR 9.7.1 and one of the IgG2a-producing variant cell lines (ICR 9.9.2.1) derived from it and discuss the advantages of an in vitro switching system for examining the dynamics of the immunoglobulin heavy chain class switch. (Author abstract) (32 Refs)

EFFECTS OF EXOGENOUS AGENTS ON CHROMOSOMES

57. ROLE OF BASE DAMAGE IN ABERRATION FORMATION: INTERACTION OF APHIDICOLIN AND X-RAYS.

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Proceedings of the Conference on DNA-Repair Chromosome Alterations and Chromatin Structure, held in Noordwijkerhout, The Netherlands, April 1981. Available from National Technical Information Service, Springfield, VA, as DE81025065:, 21 pp., 1981.

The base analog cytosine arabinoside (CA) is an inhibitor of DNA synthesis that is able to induce chromosomal aberrations not only in the DNA synthetic (S) phase of the cell cycle but in cells in the pre- (G sub 0 or G sub 1) and in the post-DNA-synthetic (G sub 2) phases of the cell cycle as well. Incubation of human peripheral lymphocytes in CA following either G sub 0 or G sub 2 x irradiation causes a synergistic increase in chromosomal aberration frequency. CA is believed to preferentially inhibit DNA polymerase alpha. It is suggested that it is inhibition of the repair of x-ray-induced base damage that is responsible for the synergistic effect on chromosomal aberration production observed with x-ray and CA treatment of human peripheral lymphocytes. It has also been observed that CA induces sister chromatid exchanges (SCE) in mammalian cells when present during normal DNA replication and that it also interacts synergistically with uv in the induction of SCE. A number of other inhibitors of DNA synthesis were also tested, one, aphidicolin (APC), did produce effects similar to CA at the same concentration. Aphidicolin is a tetracyclic diterpinoid that inhibits the growth of eukaryotic cells by inhibition of DNA synthesis. This action has been shown to result from specific inhibition of DNA polymerase alpha, but not of polymerases beta or gamma. Unlike CA, it seems likely that APC inhibits by binding to and inactivating the DNA-alpha polymerase complex. Because both CA and APC are alpha polymerase inhibitors and because both interact synergistically with uv in the production of SCE, studies were conducted to determine whether APC also shares other cytogenetic properties of CA. Results to date have shown that, like CA, APC is clastogenic in both G sub 0 and G sub 2, and it also interacts synergistically with x-rays to increase chromosomal aberration production in both G sub 0 and G sub 2. (Author abstract)

58. DEVELOPMENT OF RADIATION-'RESISTANT' CELL LINES IN VITRO AND A STUDY OF THEIR DRUG SENSITIVITIES (MEETING ABSTRACT)

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Combined Modality Therapy - Clinical and Laboratory Aspects, November 26-27, 1981, London, England British Association for Cancer Research and British Institute of Radiology; :AP.4 1981

Certain human tumors recurring after radiotherapy have shown a reduced response to subsequent chemotherapy. The aim of these studies is to determine whether exposure of tumor cells in vitro to radiation (DXR) also leads to drug resistance. Two cell lines were investigated, the murine L5178Y lymphoma and a human line (HN-1), derived from a primary squamous cell carcinoma of the tongue. The murine and human cell lines received 10 or 11 fractions of 2 Gy or 4.5 Gy per fraction respectively. This schedule for the human line attempted to mimic DXR treatment in the clinic. These DXR-treated lines were compared with the parent lines in terms of their DXR response, chromosome number, growth rates, macromolecular content and cell cycle distributions. Preliminary results indicate that DXR treatment did not appear to cause significant differences in any of these parameters. However, more detailed analyses of radiosensitivity and chromosome karyotyping are underway. Responses of the DXR-treated and parent cell lines to cytotoxic drugs are now being investigated; since no significant kinetic changes have been observed, any differences in sensitivity may represent in response of altered cell populations. Preliminary data suggest a change in response to the cytotoxic effects of bleomycin and cis-platinum after DXR treatment; other drugs being investigated are adriamycin, 5-fluorouracil, dibromodulcitol and hydroxyurea. (2 Refs)

59. PHOTODYNAMIC ACTION AND CHROMOSOMAL DAMAGE: A COMPARISON OF HAEMATOPORPHYRIN DERIVATIVE (HPD) AND LIGHT WITH X-IRRADIATION.

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Br J Cancer; 45(3):456-465 1982

Chromosomal aberrations (CA) are induced in human cells (NHIK 3025) in vitro when exposed to x-rays and to hematoporphyrin derivative (HpD) plus light. At the 0.1 survival level x-rays induce about 10x more breaks per chromosome than the photodynamic treatment. There is some evidence for non-random distribution of the CA induced by HpD plus light; ie they seem to be localized at the centromeric and telomeric regions. Such non-random distribution of CA could be explained if centromeric and telomeric chromatin were associated with the inner nuclear membrane. (Author abstract) (35 Refs)

60. PHOTOPROMOTION OF SISTER CHROMATID EXCHANGES BY PSORALEN DERIVATIVES.

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Lab. Investigative Dermatology, Rockefeller Univ., 1230 York Ave., New York, NY, 10021
Arch Dermatol Res; 272(3/4):239-244 1982

Human peripheral blood WBC exposed to UV in combination with 8-methoxypsoralen (8-MOP), 8-MOP derivatives, or 4,5'-trimethylpsoralen (TMP) derivatives were scored for sister chromatid exchanges (SCE). Flasks containing cells cultured for 24 hr were exposed to psoralen concentrations of 6.5 x 10(-8) M and UV-A irradiation (365 nanom, 0.9 Joules/cm(2)). Control cultures showed 16.5 SCE/100 chromosomes. 8-MOP was the least active SCE promoter (23.9 SCE/100 chromosomes), followed by 5'-methyl 8-methoxylpsoralen (25.7), 4-methyl-8-methoxypsoralen (27.8), and 4,5'-dimethyl-8-methoxypsoralen (31.9). TMP derivatives 4'-methoxymethyl-4,5'8-trimethylpsoralen, 4'aminomethyl-4,5'8-trimethylpsoralen-HC1, and 4'hydroxymethyl-4,5'8-trimethylpsoralen were the most active promoters (42.9, 59.1, and 75.0 SCE/100 chromosomes, respectively). Relative water insolubility, DNA binding affinity, and cross-linking ability were correlated with ability to promote SCE. (18 Refs)

61. THE EFFECT OF ULTRASOUND AND HYPERTHERMIA ON SISTER CHROMATID EXCHANGE AND DIVISION KINETICS OF BHK 21 C13/A3 CELLS.

Barrass N, Ter Haar GT, Casey G
Inst. Cancer Res., Clifton Ave., Sutton, Surrey, England
Br J Cancer; 45(Suppl5):187-191 1982

The biological effect of 3.15 megaHertz ultrasound (US) on sister chromatid exchange (SCE) frequencies and cell division kinetics was examined in a subclone of BHK 21 C13 (A3) cells. Effects of hyperthermia at 43 C, administered in conjunction with US, to cells in the G1 phase were studied. US irradiation at 37 C caused no change in the rate of cell progression. For cells irradiated with US at 43 C, only one metaphase of the 300 scored was in M3 after a sample time of 28 hr. Effects of experimental procedures on cell kinetics are discussed. Variable effects of the sampling interval were observed with regard to SCE. Despite the fluctuations in levels of SCE encountered in individual 37 C and 37 C plus US experiments, the combined data yielded almost identical statistical parameters after treatment. The results indicated that fluctuations in SCE frequencies may occur even in a relatively simple in vitro system. Despite such a finding, therapeutic levels of US had no discernible effect on SCE frequencies when administered to A3 cells in G1 at 37 C. (13 Refs)

62. EFFECT OF MALONALDEHYDE AND ACETALDEHYDE ON CULTURED MAMMALIAN CELLS. PRODUCTION OF MICRONUCLEI AND CHROMOSOMAL ABERRATIONS.

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Dept. Nutrition, Univ. Guelph, Guelph, Ontario N1G2W1, Canada
Mutat Res; 101(3):237-246 1982

The genotoxic effects of malonaldehyde (MA) and acetaldehyde (MA) and acetaldehyde (AA) were investigated using rat skin fibroblasts grown in primary culture. Production of micronuclei and aberrant chromosomes were used as indices of genotoxicity. Micronuclei were observed in cultures exposed to all concentrations of MA tested, this effect being concentration-dependent at least up to 10(-3) M. AA treatment also resulted in dose-dependent production of micronuclei, although higher concentrations were required. Treatment of the cells with MA at 10(-4) or 10(-3) M for 12 hr resulted in structural aberrations in the chromosomes, including acentric chromosomal fragments, achromatic lesions and chromatid breaks. In the case of AA, only 10(-3) M concentration produced an increase in metaphases with chromosomal aberrations. The effect of 10(-3) M AA was similar to that of 10(-4) M MA. Treatment with either aldehyde at either concentration resulted in a marked increase in the number of metaphases with structural and numerical aberrations. MA at all concentrations tested induced chromatid breaks, gaps, deletions and fragmentation. AA produced similar abnormalities but only at the higher concentration. (30 Refs)

63. POSSIBLE MECHANISM FOR CHEMICAL INDUCTION OF CHROMOSOME ABERRATIONS IN MALE MEIOTIC AND POSTMEIOTIC GERM CELLS OF MICE.

Generoso WM
Oak Ridge Natl. Lab., Oak Ridge, TN
Proceedings of the International Symposium of the Radiation Biology, held in Kyoto, Japan, September 28, 1981. Available from National Technical Information Service, Springfield, VA, as DE81031999:, 16 pp., 1981.

The mechanisms by which chemically induced lesions in the chromosomes of mammalian germ cells are actually converted to aberrations and transmitted to progeny are very complex and little understood. An attempt is made to explain how dominant-lethal mutations and heritable translocations are produced from chemical treatment of meiotic and postmeiotic germ cells of male mice. (Author abstract)

64. CYTOLOGIC AND BIOCHEMICAL GENETIC EFFECTS OF CHEMICAL CARCINOGENS.

Rasmussen RE
Dept. Community and Environmental Medicine, California Univ., Irvine, CA
Cytologic and Biochemical Genetic Effects of Chemical Carcinogens. Available from National Technical Information Service, Springfield, VA, as AD-A107 615/7:, 43 pp., 1981.

The first project is concerned with the relationship between initiation of cancer by chemicals and the damage and repair of DNA in cells and tissues susceptible to the carcinogenic action of the chemicals. The working hypothesis is that interaction of the carcinogen with cellular DNA is a necessary step in carcinogenesis and that this interaction may cause DNA damage which is then followed by DNA repair synthesis. The second project was conducted with the cooperation of the staff of the Toxic Hazards Research Unit at AMRL, WPAFB. Rats and hamsters were exposed by inhalation to hydrazine at 750 ppm for 1 hr. Groups of animals which had been exposed only once or which had been exposed 10 times were shipped to UC Irvine for study. The factors studied were (1) DNA replication in the lung; (2) DNA repair synthesis in the lung; (3) Cellular replication in the lung and nasal turbinates; and (4) Metabolism of a known lung carcinogen, 3H-benzo(a)pyrene, by lung slices from the treated animals. The third project was initiated during the current year with the goal of developing an animal model in which biochemical and cytogenetic factors could be studied during the process of tumorigenesis. Range-finding studies are underway at the Toxic Hazards Research Unit to establish the intratracheal dosage of 3-methylcholanthrene necessary to produce a high yield of lung tumors in Fischer 344 rats within 12 months. (Author abstract)

65. SELECTIVE CYTOTOXICITY OF HALOETHYLNITROSOUREAS IN CARCINOMA CELL LINE RESISTANT TO BIFUNCTIONAL NITROGEN MUSTARDS.

Tew KD, Wang AL
Dept. Biochemistry, Lombardi Cancer Center, Georgetown Univ., Washington, DC, 20007
Mol Pharmacol; 21(3):729-738 1982

Nitrosoureas with diverse carbamoylating potential were studied to estimate the cytotoxic potential of the covalent drug modification. The importance of carbamoylation to nitrosourea antitumor activity was investigated by overcoming the resistance of Walker 256 carcinoma cells to bifunctional alkylating agents. The numerical chromosomal heterogeneity between resistant cells (WR) and the parent cell line (WS) is presented. A number of marker chromosomes were present, and distinct differences between WR and WS were apparent. A comparison of the D- and L-forms of the sugar mustard showed that on a micromolecular basis 2,3,4,6-o-acetyl-N,N-bis(2-chloroethyl)-D glucopyranosylamine was more toxic to both WR and WS. The attachment of the glucopyranosylamine residue had no effect upon the resistance properties of WR cells, suggesting that possible differences in carbohydrate transport were not of relevance to the resistance phenomenon. A variety of haloethylnitrosoureas (HENU) were screened against WR and WS. For all of these drugs the resistance properties of the WR cells to bifunctional nitrogen mustards were overcome by those of HENU. The reduced cytotoxic properties of methylnitrosoureas (MNU) are presented. Approx 10-fold concentrations of MNU were required to achieve cytotoxicity similar to those of chloroethylnitrosoureas. Data suggest that in Walker 256 cells, acquired resistance to bifunctional alkylating agents can be overcome by the presence of carbamoylating agents, where these are part of a HENU or separate compounds given concomitantly with a nitrogen mustard. (38 Refs)

66. A METHOD FOR IN VIVO ANALYSIS OF SISTER CHROMATID EXCHANGES IN GASTRIC CAECA OF GRASSHOPPER.

Wu SL, Wen WN
Dept. Biochemistry, China Medical Coll., Taichung, Taiwan
Taiwan I Hsueh Hui Tsa Chih; 81(1):48-53 1982

Induction of sister-chromatid exchanges (SCES) following in vivo incorporation of 5-bromo-2'-deoxyuridine (BrdUrd) alone or with the organophosphate insecticide 2,2-dichlorovinyl-O,O-dimethylphosphate (DDVP) was analyzed in metaphase cells from the gastric caeca of adult female rice grasshoppers (Oxya formosana). BrdUrd was injected ip seven times at a concentration of 0.07 M; DDVP (10 ug/ml) was sprayed into a box containing the grasshoppers at 12 hr prior to BrdUrd injection. The method was suitable for visualization of SCEs; DDVP did not increase the rate of SCEs. (16 Refs)

67. THE INDUCTION OF SCE AND CHROMOSOMAL ABERRATIONS WITH RELATION TO SPECIFIC BASE METHYLATION OF DNA IN CHINESE HAMSTER CELLS BY N-METHYL-N-NITROSOUREA AND DIMETHYL SULPHATE.

Connell JR, Medcalf AS
Chemical Carcinogenesis Div., Inst. Cancer Res., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks HP8 4SP, England
Carcinogenesis; 3(4):385-390 1982

Chinese hamster cells (V79) were treated, either as exponentially proliferating cultures or under conditions where they were density-inhibited, with various doses of the potent carcinogen N-methyl-N-nitrosourea (MNU) or the relatively weak carcinogen dimethylsulfate (DMS). The colony forming ability of these cells and the induced frequencies of sister chromatid exchanges (SCEs) and chromosomal aberrations were assayed. Following the exposure of density-inhibited cells to radio-labeled methylating agents (labeled in the methyl group) these phenomena were related to the levels of 7-methylguanine (7-meGua), O6-methylguanine (O6-meGua) and 3-methyladenine (3-meAde) in the DNA. At equitoxic doses MNU and DMS induced similar frequencies of SCEs and chromosomal aberrations. Since, at equitoxic doses, MNU produces approx 20x more O6-meGua in V79 cell DNA than does DMS, this indicates that the formation of O6-meGua in DNA is not a major cause of SCEs and chromosomal aberrations. DMS-induced SCEs may be mediated via the production of both 3-meAde and 7-meGua in the DNA; these two methylated purines may also be responsible for MNU-induced SCEs. Therefore, no one specific methylated purine was identified as being solely accountable for the formation of SCEs. Also, the repair of lesions in the DNA of non-replication V79 cells leads to a reduction in the SCE frequency on their subsequent release from the density-inhibited state, suggesting that repair is not intimately responsible for their formation. No association was discernable between chromosomal aberrations and any of the three methylated purines studied. (Author abstract) (34 Refs)

68. LATE SIDE EFFECTS OF CHEMOTHERAPY IN OVARIAN CARCINOMA. A CYTOGENETIC, HEMATOLOGIC, AND STATISTICAL STUDY.

Einhorn N, Eklund G, Franzen S, Lambert B, Lindsten J, Soderhall S
Dept. Gynecological Oncology, Radiumhemmet Karolinska Hosp., S-104 01 Stockholm, Sweden
Cancer; 49(11):2234-2241 1982

Late side effects of chemotherapy were studied in 51 women who had received at least 300 mg of melphalan for ovarian cancer and had survived for at least 3 yr. Hematologic, statistical, and cytogenetic methods were employed. Six cases of iatrogenic leukemia were found. They appeared to represent a hematologic entity that is fairly difficult to recognize. The risk of iatrogenic leukemia in women who survived for 3 yr or more after melphalan treatment was calculated to be 950 times greater than the leukemia risk in the total female population. The cytogenetic changes were studied with three methods focused on sister chromatid exchange, chromosome aberrations, and DNA damage. The sister chromatid exchange frequency showed a marked increase, but it was corrected within a few mo. Chromosome aberrations expressed by chromosome rearrangements were increased in the peripheral lymphocytes and may persist for several yr. The frequency of DNA strand breaks was decreased indicating the presence of DNA crosslinks. Any of these types of genetic alteration could be the initiating event in carcinogenesis. (Author abstract) (31 Refs)

69. GENOTOXICITY EVALUATION OF AMSACRINE (MEETING ABSTRACT)

Lake RS, Heifetz CL, De la Iglesia FA
Department of Toxicology, Warner-Lambert/Parke-Davis Research Division, Ann Arbor, MI, 48105
Toxicologist; 2(1):175 1982

Acridinylamino derivatives constitute compounds with antineoplastic properties. Comparative genotoxicity and hence carcinogenic potential of 4'-(9-acridinylamino) methanesulphon-m-anisidide (amsacrine) was studied in several bacterial and mammalian cell in vitro assays. In a Salmonella plate incorporation assay, reverse mutation was observed only at 269 ug/plate in the nonactivation phase in frameshift tester strain TA-1537. In a preincubation modification of this assay, significantly increased revertant counts were obtained in TA-1537, TA-1535, and TA-100 at a cytotoxic dose of 672 ug/plate without S9. In the presence of S9, mutagenic activity was manifest only with TA-1537, indicating that potential base substitution activity of amsacrine was prevented more readily than its frameshift activity specific for TA-1537. At these high cytotoxic doses, a significant portion of presumed revertants did not grow in histidine-deficient medium and could have represented phenocopies. By contrast, doses as low as 0.02 ug/ml in culture medium without S9 induced a greater than five-fold increase in sister-chromatid exchange (SCE) rate and chromosomal damage frequency in Chinese hamster ovary cells in vitro. SCE response was more sensitive to S9 detoxification than the chromosomal aberration frequency. (no Refs)

70. MAMMALIAN CELL POINT MUTATION ASSAY WITH THE ANTINEOPLASTIC AMSACRINE (MEETING ABSTRACT)

Lake RS, McGuire EJ, De la Iglesia FA
Department of Toxicology, Warner-Lambert/Park-Davis Pharmaceutical Research Division, Ann Arbor, MI, 48105
Toxicologist; 2(1):173 1982

A battery of short-term in vitro tests was designed for evaluating carcinogenesis potential of the antineoplastic agent amsacrine, an acridinylamino anisidine derivative. Previous genotoxicity assays showed frameshift mutagenesis at the hisC3076 locus in Salmonella TA-1537 but no confirmed mutagenesis in TA-98, TA-100, TA-1535, and TA-1538. In Chinese hamster ovary cell assays, amsacrine induced sister-chromatid exchanges and hyperdiploid chromosomes. There are no data available on mammalian point mutation with amsacrine and a V-79 Chinese hamster lung cells assay was conducted to detect HGPRT (hypoxanthine guanine-phosphoribosyltransferase) locus mutation. Cytotoxicity was established at 2 ug/ml and one hour exposures were used with 2, 1, 0.5 and 0.25 ug drug/ml in duplicate flasks. Positive control was ethylmethane sulfonate at 800 ug/ml. Lethality occurred at 2 and 1 ug/ml. A significant number of 6-thioguanine resistant mutant colonies were induced at 0.5 and 0.25 ug/ml. The results indicate high mutagen sensitivity of this assay when compared to the dose required to induce reverse mutation in prokaryotes with a 1,000-fold separation in minimum effective dose. The evaluation of the battery of tests conducted unequivocally render a genotoxic potential. (no Refs)

71. CYTOLOGIC AND BIOCHEMICAL GENETIC EFFECTS OF CHEMICAL CARCINOGENS. ANNUAL REPORT, 1 JUL. 1980-30 JUN. 1981.

Rasmussen RE
Ohio Aerospace Medical Res. Lab., Wright-Patterson Air Force Base, OH
Sci Tech Aerosp Rep; 20(8):1128 1982

The first project is concerned with the relationship between initiation of cancer by chemicals and the damage and repair of DNA in cells and tissues susceptible to the carcinogenic action of the chemicals. The working hypothesis is that interaction of the carcinogen with cellular DNA is a necessary step in carcinogenesis and that this interaction may cause DNA damage which is then followed by DNA repair synthesis. The second project was conducted with the cooperation of the staff of the Toxic Hazards Research Unit at AMRL, WPAFB. Rats and hamsters were exposed by inhalation to hydrazine at 750 ppm for 1 hr. Groups of animals which had been exposed only once or which had been exposed 10x were shipped to UC Irvine for study. The factors studied were (1) DNA replication in the lung; (2) DNA repair synthesis in the lung; (3) Cellular replication in the lung and nasal turbinates; and (4) Metabolism of a known lung carcinogen, 3H-benzo(a)pyrene, by lung slices from the treated animals. The third project was initiated during the current year with the goal of developing an animal model in which biochemical and cytogenetic factors could be studied during the process of tumorigenesis. Range-finding studies are underway at the Toxic Hazards Research Unit (THRU) to establish the intratracheal dosage of 3-methylcholanthrene (MCA) necessary to produce a high yield of lung tumors in Fischer 344 rats within 12 mo. (Author abstract)

GENERAL REVIEWS

72. GENETIC INFLUENCES IN HUMAN TUMORS.

Knudson AG
Graduate Sch. Biomedical Sciences, Univ. Texas Health Science Center, Houston, TX
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Genetic states predisposing to cancer include chromosomal disorders such as Down's syndrome and Klinefelter's syndrome with increased risks of leukemia. The syndromes of Fanconi and Bloom are both autosomal recessive disorders which predispose to leukemia and cancer. Ataxia-telangiectasia is another autosomal recessive disease associated with chromosomal abnormality and a strong predisposition to lymphoid neoplasia. Xeroderma pigmentosum is a genetic state which predisposes to environmentally induced skin cancer. Dominantly inherited tumors differ sharply from the genetic conditions previously discussed in that tumor is a critical phenotypic feature and occurs with high penetrance. In some instances, a tumor is part of a syndrome, other manifestations of which are other kinds of tumors or nonneoplastic signs. In other instances tumor occurs in just one tissue, although it may be multiple in that tissue. Tumor syndromes include polyposis of the colon, Gardner's syndrome, hereditary adenocarcinomatosis, basal cell nevus syndrome, multiple endocrine tumor syndromes, neurofibromatosis, von Hippel-Lindau syndrome and tuberous sclerosis. Specific tumors which are inherited but not part of a syndrome are retinoblastoma, Wilms' tumor of the kidney and neuroblastoma. (57 Refs)

73. CYTOGENETICS.

Nowell PC
Dept. Pathology, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Present knowledge in the field of chromosome alterations in tumor cells is reviewed and the significance of certain findings is discussed. Human leukemias have been more extensively studied cytogenetically than any other group of tumors and have provided much of the data upon which three generalizations about malignancy and cytogenetics are based. These general statements based on leukemia research are that most tumors are chromosomally abnormal, that chromosome alterations are often the same in all cells of a given tumor, and that neoplasms of a particular type do not show a consistent cytogenetic alteration from one tumor to another. A specific change occurring in nearly every tumor of a given type, such as the Philadelphia chromosome in human chronic granulocytic leukemia is the exception, rather than the rule. Nearly all human malignant solid tumors studied to date have shown chromosome abnormalities with only a few cases reported in which the karyotype appeared normal. In addition to human leukemias and solid tumors, other areas reviewed are chromosome breakage and cancer, cytogenetics of cells in culture, animal tumors, and a discussion of chromosome changes and tumor initiation and progression. The clinical applications of tumor chromosome studies include the diagnostic use of chromosome data to aid in the classification of confusing cases of human leukemia. (206 Refs)

74. MEANING OF CHROMOSOMAL ABNORMALITY IN LEUKEMIA.

Tomonaga Y, Sadamori N, Matsunaga M, Tagawa M, Ichimaru M
Dept. Internal Medicine, Medical Inst. for Post, Atomic Bomb Disorder, Attached to Nagasaki Univ. Sch. Medicine, Nagasaki, Japan
Nippon Rinsho; 39(8):2773-2779 1981

The findings primarily obtained in the examination of chromosome stained with the bone marrow direct method are described. The highly disease specific chromosomal abnormality, the Philadelphia chromosome (Ph1) is a small marker chromosome, and found in 90% of chronic myelocytic leukemia (CML). Ph1 exists prior to the appearance of clinical symptoms of CML, and the Ph1 clone still remains in remission after therapy; in contrast, the abnormal clone disappears in complete remission of acute leukemia. When CML converts into the acute state, new chromosomal abnormalities in addition to Ph1 appear in 75 - 80% of the cases. Therefore, it can be a criteria for the early diagnosis of acute state conversion. In combining with examination of clinical types of acute state conversion, leukemia cell types, immunological markers, and terminal deoxynucleotidyl transferase activity, Ph1 and additional other chromosomal abnormalities can be used for the estimation of prognosis and selection of therapy. Clones with chromosomal abnormalities can be found in about 50% of acute non-lymphocytic leukemia, but a common marker such as Ph1 in CML is not yet known. However, some close correlation between disease type and chromosomal abnormality is beginning to show up after application of differential chromosome staining method. Two well known such chromosomal abnormalities are 8; 21 translocation and 15; 17 translocation, the former is seen in acute myelocytic leukemia and the latter in acute premyeloblastic leukemia. Other chromosomal abnormalities and their possible association with diseases such as preleukemia, and myeloproliferative syndromes are described. (27 Refs) (In JPN)

75. OTHER LEUKEMIAS AND RELATED DISEASES: ON HEMOPOIETIC DYSPLASIA AND CHRONIC MYELOPROLIFERATIVE DISORDERS.

Sawada H, Yamagishi H, Uchino H
First Dept. Internal Medicine, Kyoto Univ. Sch. Medicine, Kyoto, Japan
Nippon Rinsho; 39(8):2749-2755 1981

Preleukemic state are characterized by specific blood abnormalities prior to the clinical confirmation of leukemia. Prospectively, hematological abnormality similar to preleukemia state will not be a necessary condition for transformation into leukemia. Hemopoietic dysplasia (HD) is defined as a panmyelopathy presenting abnormality in all three lines of hematopoietic cells, and leads eventually to leukemia. HD should not be confused with the myelodysplastic syndrome at this time. Erythroleukemia mainly shows abnormal formation of erythrocytic hematopoietic tissue and of other cell lines, such as granulocytic cells. Refractory anemia with excess of myeloblasts (RAEM) is found more in 60-70-yr-old people, and morphologically shows abnormality in the three myelocytic cell lines. Chronic myelomonocytic leukemia is similar to RAEM but no increase of monocytic immature cells is seen. Idiopathic myelofibrosis is characterized by osteosclerosis accompanied by extramedullary hematopoiesis. Polycythemia vera shows an increase in the peripheral erythrocytes and in the blood volume. Primary thrombocythemia differs from chronic myelocytic leukemia in the negative Philadelphia chromosome and in the high NAP. Acute myelofibrosis shows increase in megakaryocytes and megakaryoblasts without splenomegaly. Relationship among the above disorders is discussed. (28 Refs) (In JPN)

76. QUANTITATIVE CYTOLOGY IN MYELOMA RESEARCH.

Barlogie B, Latreille J, Alexanian R, Swartzendruber DE, Smallwood L, Maddox AM, Raber MN, Drewinko B

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Clin Haematol; 11(1):19-46 1982

The role of quantitative cytology in myeloma research is discussed. Cytometric probes applicable to myeloma research include markers of neoplasia or tumor differentiation and cytokinetic descriptors. DNA content measurements may provide prognostically relevant information on intrinsic tumor cell properties such as ploidy and proliferative activity. Additional methods of characterizing the minor proportion of diploid plasma cells include analysis of RNA, overall protein, cytoplasmic Ig, and nucleolar antigen content. Cytokinetic marker techniques include DNA specific probes, DNA denaturation, and quenching of DNA probes. (58 Refs)

77. CYTOGENETICS OF MALIGNANT LYMPHOMAS.

Fonatsch C

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Dtsch Med Wochenschr; 107(12):468-471 1982

Methods and findings of cytogenetic analysis of malignant lymphomas (ML) are reviewed. Analysis consists of counting and structural examination of chromosomes using fluorescence or Giemsa banding techniques. Specific abnormalities characteristic of ML include loss or gain of certain chromosomes, presence of specific chromosomal alterations, and increased frequency of rearrangements of specific chromosomal regions. The most common extra chromosomes found in lymphomas are chromosomes 7, 3, and 12. The most common structural change is the marker 14q+, found in 64% of all lymphomas. Epstein-Barr virus (EBV) apparently is linked to chromosome 14, although the 14q+ marker is also found in EBV-negative lymphomas. Chromosome 14 is apparently involved in control of cell proliferation. Other chromosomes frequently showing alterations in lymphomas are 1, 6, and 11. Chromosome 1 is of particular importance in myeloid lymphomas. Chromosomal rearrangement alters gene function by a position effect. ML cells show a rate of sister chromatid exchange double of that found in normal cells, indicating chromosomal instability. Cytogenetic analysis can be used to differentiate ML from other lymphatic disorders. Staging of ML is aided by detection of chromosomal abnormalities in otherwise apparently normal biopsy tissue. Presence or absence of particular anomalies is of prognostic value, especially in cases of B-cell acute lymphatic leukemia and hairy-cell leukemia. (18 Refs) (In GER)

78. SOMATIC CELL GENETIC ANALYSIS OF THE NEOPLASTIC STATE (MEETING ABSTRACT)

Ruddle FH
Department of Biology, Yale University, New Haven, CT
Thirty-fifth Annual Symposium on Fundamental Cancer Research, March 2-5, 1982, Houston, Texas. The University of Texas M. D. Anderson Hospital and Tumor Institute 38 pp., 1982.

Somatic cell genetics allows a direct means of dissecting the genetic constitution of neoplastic cells. Three examples of the potential of this approach will be discussed. In the first, recent data on the assignment of Abelson and Moloney 'ONC' genes in mice will be described. The assignment of the entire ONC gene system can be readily accomplished by restriction fragment mapping. Somatic cell genetic systems also lend themselves to the mapping of genes that specify surface antigens. Addressing the second experimental system, we will discuss the assignment of the human specific antigen of 3-methylcholanthrene-induced mouse sarcoma. This gene has been mapped to mouse chromosome 12 in proximity to the immunoglobulin heavy-chain locus. Recent work relating this genetic locus to mechanisms regulating chromosome segregation in mouse x Chinese hamster hybrids will be described. The third system described is a gene transfer system for testing the expression of surface antigen-coding genes. Specifically, cloned genes of the human major histocompatibility locus have been transferred into murine cells where they are expressed with high efficiency. More generally, we show this system's potential for analyzing genetic mechanisms that control the expression of surface antigens in the context of either normal or atypical growth. (no Refs)

79. MUTAGENESIS ASSAY METHODS.

Casciano DA
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Food Technol; 36(3):48-50,52 1982

Submammalian, as well as several in vitro and in vivo mammalian mutagenesis assay systems currently being used or developed to detect potential mutagens or carcinogens are described and discussed, with particular regard to advantages and disadvantages of each system. Bacterial systems are most useful as prescreens to detect mutagens capable of inducing point mutations and to identify the type of lesion induced at the molecular level. They are inexpensive, rapid, and easily adapted to inclusion of exogenous metabolic activation systems, but they are not readily amenable to detection of chromosome aberrations and results are difficult to extrapolate to man. Uses, advantages, and disadvantages of in vitro mammalian systems are similar to those of submammalian systems, although the former have the advantage of having a mammalian genome as the target molecule. Use of the intact mammal in mutagenicity/carcinogenicity testing provides the closest approach to metabolic conditions in humans. These include the 'spot' test, micronucleus test, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal, heritable translocation, phenotypic specific locus, and biochemical specific locus. (18 Refs)

80. TESTS FOR ASSESSING THE MUTAGENIC ACTION OF DRUGS IN MAN.

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Insitut fur Genetik, Freie Universitat Berlin, Arnimallee 5-7, D-1000 Berlin 33, W. Germany
Prax Klin Pneumol; 35(Suppl1):1027-1033 1981

Cultures of human peripheral-blood lymphocytes are used for routine, rapid testing of mutagenicity. Lymphocytes are stimulated to undergo mitosis in vitro. Mitotic chromosomes are then examined for aberrations such as sister chromatid exchanges, dicentric chromosomes, and fragmentation. Findings are used to predict the effects of potential mutagens in humans. Problems of in vitro testing and alternative methods of testing are discussed. (17 Refs) (In GER)

81. CHEMICAL CARCINOGENESIS: INTERACTIONS OF CARCINOGENS WITH NUCLEIC ACIDS.

Rajalakshmi S, Prema M, Sarma D
Dept. Pathology, Univ. Toronto, Toronto, Ontario, Canada
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

The nature of modified nucleic acids following interactions with carcinogens is reviewed. Interactions of chemical carcinogens with DNA include covalent interactions such as alkylating agents, nitrosamines and nitrosamides, and noncovalent interactions of both internal and external binding types. Purine-N-oxides and many inorganic metal compounds are known to be carcinogenic. The use of fractionation techniques has revealed that carcinogens exhibit a preferential interaction with some regions of DNA in chromatin. Interactions of chemical carcinogens with RNA have been studied, and alterations in RNA have been attributed to alkylating agents such as nitrosamines and nitrosamides, to urethan, to aromatic amines and amides, and to polycyclic aromatic hydrocarbons. Interactions of carcinogens with nucleic acids exert a profound effect on the structure and synthesis of DNA and RNA, gene expression, and regulation of cellular development. Although the exact mechanism or mechanisms by which DNA damage and repair are involved in carcinogenesis is not completely understood, there is overwhelming evidence indicating a causal relationship between these two processes. (634 Refs)

82. SEQUENTIAL ANALYSIS OF THE SAME BLADDER AND PROSTATE CELLS BY FLOW CYTOMETRY AND IMAGE ANALYSIS (MEETING ABSTRACT)

Tanke HJ, Ploem JS, Jonas U
No affiliation given
77th Annual Meeting of the American Urological Association, Inc May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

In the field of analytical cytology one distinguishes two main techniques for the quantitative analysis of cells: flow cytometry and image analysis. These analytical techniques are increasingly applied to obtain objective quantitative information on cells, for improved cytological diagnosis or prognostic information on cancers. In case of bladder and prostate cytology, flow cytometry has proven to be useful for fast measurements of DNA and RNA and immunological properties. Image analysis is used to automatically detect and classify cells on the basis of DNA content, chromatin distribution, shape, nuclear-cytoplasmic ratio etc. Both approaches have their intrinsic advantages and limitations. The combination of flow cytometry and image analysis, therefore is a powerful analysis technique in urinary cytology. To realize this combination prostate and bladder cells of interest were sorted out after flow cytometry (FACS IV) by electrostatic deflection. From the sorted fractions preparations were made and restained for image analysis with the LEYTAS system. This system offers the completely automatic analysis of entire microscopic fields by image transformation procedures. Abnormal cells are detected and stored in image memories for either visual inspection by the cytologist, or for further automated analysis of for instance the chromatin distribution by software procedures. (no Refs)

83. COLOR ATLAS OF CANCER CYTOLOGY.

Takahashi M
Dept. Pathology, Gifu Univ. Sch. Medicine, Gifu, Japan
Color Atlas of Cancer Cytology. Tokyo, Igaku-Shoin, 575 pp., 1981.

General cancer cytology (GCC), fundamental knowledge of cytology, laboratory techniques which are necessary for routine practice and occasionally available for research work, and practical cytology (PC) that is applied to various organs and tissues are presented. The technique of preparing smears is described and normal and atypical cytology is reviewed with particular reference to histopathology. Mitosis, normal cell constituents in exfoliative cytology, criteria of malignancy, differentiation, dedifferentiation, dyskaryosis, dyskeratosis, cellular alteration simulating malignancy, practical screening, diagnostic classification, cellular degeneration in exfoliative cytology, cell typing of malignant cells, preparation and fixation of smears, radiation cell changes, fluorescence microscopy, differential interference contrast microscopy, human chromosomes, X and Y chromatin, and cytochemical approach to isoenzyme related to malignancy comprise GCC. PC of the female genital tract, the breast, the respiratory and alimentary tracts, CNS, effusions in body cavities, the urinary tract, lymph nodes, the skin and its related mucous membrane, and bone and bone marrow are discussed. Histopathological criteria of tumors have been represented by anaplasia of tumor cells, invasive growth destroying and replacing the surrounding normal tissues, rapid autonomous growth, and metastases by way of lymphatic permeation and blood vascular permeation and implantation. (1793 Refs)

84. SISTER CHROMATID EXCHANGE FORMATION.

Latt SA
Div. Genetics, Mental Retardation Center, Children's Hosp. Medical Center, Boston, MA, 02115
Annu Rev Genet; 15:11-55 1981

Sister chromatid exchanges can be detected either by autoradiography or by BrdU-dye techniques. SCE analysis is useful both for detecting mutagenic carcinogens and for investigating certain hereditary diseases that predispose to neoplasia. Examination of factors capable of modifying the SCE response, as well as phenomena that correlate with SCE formation, provides clues about molecular events involved in sister chromatid exchange. Limited analogy between SCEs and other processes involving DNA interchange can be drawn, but both the mechanism and the biological significance of SCE formation remain largely unknown. (Author abstract) (337 Refs)

85. INDUCTION OF CHROMOSOME ABERRATIONS IN GERM CELLS: A DISCUSSION OF FACTORS THAT CAN INFLUENCE SENSITIVITY TO CHEMICAL MUTAGENS.

Preston RJ
Oak Ridge Natl. Lab., Oak Ridge, TN
Proceedings of the International Conference on Environmental Mutagens, held in Tokyo, Japan, September 20, 1981. Available from National Technical Information Service, Springfield, VA, as DE82002797:, 13 pp., 1981.

The intent of this presentation is to discuss the relationships between induced and observed (or recovered) chromosome aberration frequencies, particularly in different germ cell stages following treatment with chemical mutagens. There are many factors that can influence both the induced and observed frequencies, such as the cell cycle stage at the time of treatment and observation, and the extent and relative rates of DNA repair in different cell types. These factors are discussed, often with reference to in vitro cell systems, in an attempt to present a general model of sensitivity to chromosome aberration production by chemical mutagens. (Author abstract)

86. NATURE AND MECHANISM OF INDUCTION OF MUTATIONS. ANNUAL PROGRESS REPORT, AUGUST 1, 1980-OCTOBER 1, 1981.

Nilan RA, Kleinhofs A, Konzak CF
Washington State Univ., Pullman, WA
Nature and Mechanism of Induction of Mutations. Annual Progress Report, August 1, 1980-October 1, 1981. Available from National Technical Information Service, Springfield, VA, as DE82001743:, 11 pp., 1981.

New knowledge of the mechanism of mutation induction and the nature of mutations in eukaryotes continues to be developed from experiments involving sodium azide. Azide is a potent mutagen in bacteria and in higher plants but it is weakly mutagenic and not carcinogenic in mammalian systems. It was determined that azide acted through a promutagen or organic metabolite both in barley and bacterial cells. This metabolite has been isolated and characterized. During the past year, considerable progress has been made in understanding the pathway by which the metabolite is synthesized in barley and bacteria. It can be synthesized in vitro both in bacteria and barley and some additional knowledge of the structure of the metabolite is being revealed through chemical synthesis of the metabolite. Additional information concerning the lack of azide mutagenicity in mammalian cells has been developed through the detailed studies of the action of azide and its metabolite from bacteria and barley on sister-chromatid exchanges in mammalian cells. Neither azide nor its metabolites of bacteria and barley are particularly effective, and to date no metabolite has been detected in mammalian cells. Azide-induced mutants in barley have been utilized in barley improvement, in probing the pathways of a number of biochemical and physiological processes and in understanding the structure of gene loci and the nature of mutations induced. (Author abstract)

87. REPAIR OF RADIATION DAMAGE IN MAMMALIAN CELLS.

Setlow RB
Brookhaven Natl. Lab., Upton, NY
Repair of Radiation Damage in Mammalian Cells. Available from National Technical Information Service, Springfield, VA, as DE81030824:, 16 pp., 1981.

The responses, such as survival, mutation, and carcinogenesis, of mammalian cells and tissues to radiation are dependent not only on the magnitude of the damage to macromolecular structures - DNA, RNA, protein, and membranes - but on the rates of macromolecular syntheses of cells relative to the half-lives of the damages. Cells possess a number of mechanisms for repairing damage to DNA. If the repair systems are rapid and error free, cells can tolerate much larger doses than if repair is slow or error prone. It is important to understand the effects of radiation and the repair of radiation damage because there exist reasonable amounts of epidemiological data that permits the construction of dose-response curves for humans. The shapes of such curves or the magnitude of the response will depend on repair. Radiation damage is emphasized because: (a) radiation dosimetry, with all its uncertainties for populations, is excellent compared to chemical dosimetry; (b) a number of cancer-prone diseases are known in which there are defects in

DNA repair and radiation results in more chromosomal damage in cells from such individuals than in cells from normal individuals; (c) in some cases, specific radiation products in DNA have been correlated with biological effects, and (d) many chemical effects seem to mimic radiation effects. A further reason for emphasizing damage to DNA is the wealth of experimental evidence indicating that damages to DNA can be initiating events in carcinogenesis. (Author abstract)

88. RECENT DEVELOPMENTS IN THE MECHANISMS OF DNA REPAIR AND IN THE ROLE OF DNA REPAIR IN CHEMICAL CARCINOGENESIS AND CANCER CHEMOTHERAPY.

Roberts JJ
Inst. Cancer Res., Royal Cancer Hosp., Pollards Wood Res. Station, Chalfont St. Giles, Bucks., HP8 4SP, England
Adv Exp Med Biol; 136(partB):1367-1387 1982

Mechanisms of DNA repair, including excision repair, and the role of DNA repair in chemical carcinogenesis and cancer chemotherapy are discussed. Base excision (small patch repair) and nucleotide excision (large patch repair) are described and a two-step model for excision repair of pyrimidine dimers is illustrated. Whether any specific excision repair enzyme acts similarly on UV- and chemically-induced DNA damage to remove a modified base by glycosylase action is unproven. Inducible excision repair processes in prokaryotic cells (adaptation and SOS repair) and in mammalian cells is discussed. Reactivity of compounds can be correlated with mutagenicity and carcinogenicity: agents that react by a unimolecular substitution reaction (SN1) are the most potent mutagens and the most potent carcinogens. SN1 reactivity in turn correlates with the ability of compounds to react more extensively with the oxygen atom sites in DNA. The physiological state of a tissue determines not only the degree of cell proliferation taking place, but also the cytotoxic effect of DNA lesions that modify or act as a block to DNA replication. DNA excision repair and cytotoxicity is discussed. Normal cells may be proficient in repair of alkylation damage, while tumor strains may be either proficient or deficient in repair. Replication of DNA on a damaged template (RDT), or post-replication repair, occurs when unexcised DNA damage is circumvented during replication. In rodent cells, RDT may be adversely influenced by post-treatment incubation in the presence of caffeine. RDT may occur by gapped synthesis or replicative bypass (branch migration). Base mispairing and the introduction of potentially mutagenic lesions has been implicated in the etiology of nitrosamine-induced carcinogenesis. (68 Refs)

89. POSSIBLE ROLE OF GENE AMPLIFICATION IN MALIGNANCY (MEETING ABSTRACT)

Schimke RT
Department of Biological Sciences, Stanford University, Stanford, CA
Thirty-fifth Annual Symposium on Fundamental Cancer Research, March 2-5, 1982, Houston, Texas. The University of Texas M. D. Anderson Hospital and Tumor Institute 38 pp., 1982.

Gene amplification as a mechanism for increasing the synthesis of a cellular protein in somatic cells of higher organisms has received little attention. New studies concern the acquisition of drug resistance in cultured animal cells, reversion of auxotrophy in which the defect results from a catalytically defective enzyme, and amplification in development time. The amplifications can be either stable or unstable and are associated with chromosomal or extrachromosomal localization of the amplified genes. The karyological consequences of gene amplification are analogous to observed abnormalities in chromosomes in solid tumors and cell lines derived from solid tumors, ie, expanded chromosome regions and double minute chromosomes. The question of whether these abnormalities constitute amplified genes arises, the consequence of which would be an increased potential for cells to overcome normal growth constraints and immune surveillance processes, ie, malignancy or malignant progression. The frequency with which cultured animal cells (mouse and hamster) become resistant to methotrexate can be increased by pretreating the cells with a variety of agents, including inhibitors of DNA replication, ultraviolet light, and acetoxyacetylaminofluorene. Thus, if the development of malignancy is associated with increased production of normal cellular products, gene amplification is one such mechanism. Indeed, in bacteria the most common mechanism for increasing the amount of a protein is not an 'up-promoter' mutation, but rather gene duplication. The question, therefore, is whether this may not also be the case in somatic cells. (no Refs)

OTHER RELATED STUDIES

90. RESPONSE OF A BLAST CRISIS OF CGL TO INTERFERON-ALPHA (MEETING ABSTRACT)

Hill NO, Khan A, Pardue A, Aleman C, Hilario R, Hill JM
Wadley Institutes of Molecular Medicine, Dallas, TX, 75235
Proc Am Soc Clin Oncol; 1:C-499 1982

Two patients with blast crisis of chronic granulocytic leukemia treated only with high dose intravenous human leukocyte interferon showed objective responses to this therapy, as did one additional patient with Philadelphia chromosome positive chronic granulocytic leukemia without blast crisis. The first patient initially received 500,000 units of interferon/kg daily in four divided doses. This resulted in a 95% decrease in blasts in 23 days of treatment. The second patient in blast crisis had a decrease in total white cells from a peak of 78,000 to 7,800 after three weeks of therapy at 1 million units/kg per day IV. Blasts decreased from a total of 10,800 to 73 absolute blasts/ul in that time. The patient without blast crisis had a decrease in the total white count from 94,000 to 21,000 as well as a reduction in spleen size. (no Refs)

91. THE CONSTRUCTION OF COSMID LIBRARIES OF EUKARYOTIC DNA USING THE HOMER SERIES OF VECTORS.

Chia W, Scott MR, Rigby PW
Cancer Res. Campaign, Eukaryotic Molecular Genetics Res. Group, Imperial Coll. Science and Technology, London SW7 2AZ, England
Nucleic Acids Res; 10(8):2503-2520 1982

We have constructed and characterized a series of approved, disabled cosmid vectors which we call Homer cosmids and have examined the optimal conditions for the construction of libraries of eukaryotic DNA segments using these vectors. Analysis of these libraries shows that most of the sequences we have tested for are present at the expected frequency and that the libraries can be stably propagated. We have also directly tested the stability of cosmid clones carrying tandemly repeated inserts. This work shows that it should be possible to clone most eukaryotic genes using cosmid vectors and that such cloning systems have considerable advantages over those more commonly used. (Author abstract) (51 Refs)

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CLINICAL STUDIES OF CHROMOSOMES IN HUMAN CANCER

1. CYTOLOGICAL AND CYTOGENETICAL STUDIES ON HUMAN MENINGIOMA.

Zang KD
Inst. Human Genetics, Univ. Saar, 6650 Homburg, W. Germany
Cancer Genet Cytogenet; 6(3):249-274 1982

Characteristics of meningiomas which make them a model system for the study of human cancer development are described. Meningiomas show a remarkably good correlation between karyotype and histological and growth patterns which particle cultures of the individual tumors develop in vitro. Histological classification of meningiomas is described. In contrast to true brain tumors, meningiomas occur most offten in the fifth and sixth decade of the life and occur twice as frequently in females as in males. Characterization of meningiomas according to their respective karyotype shows a highly significant shift in sex distribution. In tumors with normal karyotypes, the male:female sex ratio is 1:3 while in more aberrant forms the ratio is approx 1:1. Chromosomal indications for virus involvement in the etiology of meningiomas are present-

HE 20.3173/2:

ed along with immunofluorescence data, induction of virus particles, and demonstration of episomal Simian virus 40 (SV40) DNA in meningiomas. Experimental transformation of meningioma cell cultures and fibroblast cultures of the same patients with SV40 is described. (62 Refs)

2. TYPE-SPECIFIC COMBINATIONS OF KARYOLOGIC FEATURES IN HUMAN BRAIN TUMORS (MEETING ABSTRACT).

Low WF, Muller HA

Pathologisches Institut der Universitat, Abt. f angewandte Cytologie, 8700 Wurzburg, W. Germany

Deutscher Kongress fur Zytologie, June 15-16, 1981, Karlsruhe, W. Germany. Deutsher Kongress fur Zytologie 55 pp., 1981.

Imprint cytology studies of human brain tumors should clarify whether tumor or tissue specific chromatin distribution patterns are present in the cell nuclei of various types of tumors. It turned out that the cell nuclei of different kinds of tumors do have their own characteristic features with respect to nuclear shape, chromatin structure and nuclear size. In this way it is possible to recognize as such, eg, astrocytomas, oligodendrogliomas, and ependymomas as well as meningiomas and neurinomas by imprint cytology on the basis of combinations of karyologic features and to distinguish them from one another. Variations in type-specific nuclear features, as occur for instance in anaplastic astrocytomas, represent the morphologic expression of a loss of differentiation in such tumors. In malignant gliomas which cannot be classified more precisely, lastly, combinations of karyologic features, as they can in glioblastoma multiforme as well, provide some idea as to the cell origin of the tumor so long as it is not completely undifferentiated. (no Refs) (In GER)

3. HUMAN LARGE-BOWEL CANCER: CORRELATION OF CLINICAL AND HISTOPATHOLOGICAL FEATURES WITH BANDED CHROMOSOMES.

Reichmann A, Levin B, Martin P

Dept. Medicine, Section Gastroenterology, Univ. Chicago, Box 400, 950 East 59th St., Chicago, IL, 60637

Int J Cancer; 29(6):625-630 1982

Clinical and histopathological features were correlated with cytogenetic banding studies on direct preparations from 31 large-bowel tumors. An interesting relationship between the site and the karyotypes of the tumors was observed. There appears to be a progressive increase in chromosomal number and/or structural rearrangement as one progresses from proximal to distal large bowel. We suggest that these observations may be related to differences in function and micro-environment within different areas of the colon. Although it is not known what factors favor cytogenetic variability and instability on the left side or the presence of fewer abnormalities on the right side of the colon, it is evident that clonal karyotypic evolution may be important in the progression of large-bowel cancer. The brevity of follow-up precludes conclusions regarding the influence of karyotype on survival. (Author abstract) (18 Refs)

4. HEMATOPOIETIC DYSPLASIA AND MARROW HYPOCELLULARITY IN CHILDREN: A PRELEUKEMIC CONDITION.

Kobrinsky NL, Nesbit ME, Ramsay NK, Arthur DC, Krivit W, Brunning RD

(c/o Brunning), Univ. Minnesota, Box 198, Mayo Memorial Building, 420 Delaware St. S.E., Minneapolis, MN, 55455

J Pediatr; 100(6):907-913 1982

Seven children with hematopoietic dysplasia were identified by morphologic criteria. The peripheral blood and bone marrow findings in these children were characterized by macro-ovalocytosis, progressive marrow hypoplasia, proteinaceous debris in the marrow interstices, and megaloblastoid changes. Six of the patients had major constitutional abnormalities including coarse or unusual facies (4), short stature (4), and mental retardation (4). These children were prone to recurrent bacterial infections prior to the onset of documented leukopenia. Chromosome studies of blood and bone marrow demonstrated a clonal abnormality involving the B, C, and E groups in 3/5 patients. An increase in the number of spontaneous chromosome breaks or radial figures was not observed. CFU-Cs were uniformly decreased in 5/5 patients, prior to the onset of leukopenia in one. Incomplete and transient responses to folic acid (3/4), androgens (1/4), and steroids (3/3) were noted. There were no responses to vitamin B12 in three patients or to ATG or other immunosuppressive therapies in four patients. One child has a sustained response to pyridoxine and one has had successful hematopoietic reconstitution by bone marrow transplantation. Three of the patients developed myelogenous leukemia 13, 47, and 100 mo, respectively after presentation. Two have died from leukemia and one from intracranial hemorrhage. Children with HD differ morphologically and clinically from adults with 'the preleukemic syndrome' by manifesting marrow hypocellularity and constitutional abnormalities. Both groups are at high risk for the development of progressive pancytopenia and myelogenous leukemia. Unlike those with Fanconi anemia, these children respond poorly to treatment with androgens and steroids. Results of bone marrow transplantation in one of the patients are encouraging. (Author abstract) (20 Refs)

5. SISTER CHROMATID DIFFERENTIATION AND CELL-CYCLE-SPECIFIC PATTERNS IN CHRONIC MYELOCYTIC LEUKEMIA AND NORMAL BONE MARROW.

Becher R, Schmidt CG

Innere Universitatsklinik (Tumorforschung), D-4300 Essen 1, W. Germany

Int J Cancer; 29(6):617-620 1982

After in vitro incubation with bromodeoxyuridine (BrdUrd)-containing medium, metaphases of Philadelphia (Ph1)-chromosome positive cells in the blood and/or bone marrow of eight untreated patients with chronic myelocytic leukemia (CML) were analyzed by means of sister chromatid differentiation (SCD) and compared to 10 normal bone marrows. The majority of proliferating Ph1-positive cells (range: 46-86%) were unable to complete more than one cell cycle during the culture period of 50 hr (M1 metaphases). Ph1-positive M2 metaphases which had completed two cell cycles were found in the range of 18-54% and almost no M3 metaphases were detected after passage through three cell cycles (0-1%). The corresponding findings in proliferating normal bone-marrow cells were: M1 (13-68%), M2 (30-79%) and M3 (0-18%). These data support the notion that there is a prolonged cell cycle time in CML which can be measured by SCD, demonstrating a proportional shift from M3/M2 to M1 metaphases. SCD is suggested for kinetic studies on human malignant cell clones characterized by marker chromosomes. (Author abstract) (18 Refs)

6. SISTER CHROMATID EXCHANGE AND GROWTH KINETICS IN CHRONIC MYELOID LEUKEMIA.

Stoll C, Oberling F, Roth MP
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Cancer Res; 42(8):3240-3243 1982

The frequency of sister chromatid exchange (SCE) was analyzed in bone marrow cells of 16 patients with chronic myeloid leukemia. We have compared the SCE frequency in these patients, in both chronic and blastic phases of the disease, to that of normal individuals. The frequency of SCE in blastic-phase chronic myeloid leukemia patients (mean, 1.86/cell) was significantly lower than that in chronic phase (mean, 2.96/cell), which was in turn lower than that in normal individuals (mean, 4.108/cell). We have used the SCE data to compare the rates of division of the bone marrow cells. Cells from chronic myeloid leukemia patients divided more slowly than did those from normal individuals, those from blastic-phase patients being slowest. (Author abstract) (31 Refs)

7. SISTER CHROMOSOME EXCHANGE IN LEUKOSES (MEETING ABSTRACT).

Becher R, Schmidt CG
Innere Klinik und Poliklinik, Universtatsklinikum Essen, Essen, W. Germany
Onkologie; 4(5):276 1981

Sister chromatid exchange (SCE) can be made visible by light microscopy after double-stranded incorporation of the thymidine analog bromodeoxyuridine (BrdU) into chromosomal DNA. The frequency of SCE has proven to be the most sensitive parameter reflecting exposure to mutagenic agents and provides an indication of genome instability in Blooms syndrome. In the preceding paper we reported on the frequency of spontaneous SCE in 8 acute leukoses and 12 cases of Philadelphia chromosome positive chronic myeloid leukemia (CML). Freshly obtained cell material (bone marrow and/or peripheral blood) was incubated in RPMI 1640 medium for 50 hr and for the last 2 hr of the culture period treated with colcemid. The SCE rate in AL was between 2.11 and 2.97 instances of exchange per cell and in CML between 2.32 and 3.44. The deviation from normal bone marrow (3.64-5.15) is statistically significant. (no Refs) (In GER)

8. FURTHER CYTOGENETIC STUDIES ON ACUTE PROMYELOCYTIC LEUKEMIA.

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Cancer Genet Cytogenet; 6(1):39-46 1982

Chromosomes were analyzed in nine cases of acute promyelocytic leukemia (APL-M3), including a follow-up case and an erroneously diagnosed case from our previous reports. The reciprocal 15; 17 translocation, t(15q+; 17q-), was found in all cases, and the break points were estimated to be 15q22 or q23 and 17q12. In addition, trisomy 8 and an isochromosome of the long arm of the affected chromosome number 17, i(17q-), were observed in two cases each. Some other abnormalities were encountered, mostly in remission or relapse. The disappearance and repopulation of t(15q+; 17q-) cells were associated with complete remission and relapse, respectively, in two repeatedly analyzed cases. Including the previously reported cases, we investigated a total of 12 cases of APL, and all were found to be associated with t(15q; 17q-). The mean age of the 12 patients was 34.25 +-3.12 (SD) yr, and their mean survival 266.3 +- 95.67 (SD) days. (Author abstract) (22 Refs)

9. CLONAL EVOLUTION IN RELAPSE OF ACUTE LYMPHOBLASTIC LEUKEMIA.

Hayashi Y, Kaneko Y, Abe R, Sakurai M
Hematology Clinic, Saitama Cancer Center, Saitama, Japan
Rinsho Ketsueki; 22(10):1545-1551 1981

Chromosome karyotypes were determined in 22 cases of acute lymphoblastic leukemia, and sequential cytogenetic studies were performed in 5/22 (3 men, 2 women; 15-48 yr old) who had achieved remission but later had recurrence. Detailed studies were not possible in one patient who had tetraploid leukemia cells at diagnosis and after relapse. Cell samples were obtained by direct marrow aspiration or unstimulated culturing of peripheral blood. Chromosomal analysis was performed using common Giemsa staining techniques, Caspersson et al Q chromosome method, or Sanchez et al simple G-banding technique. Six clonal evolutions were observed in four patients, and death occurred soon after the discovery of the clonal evolutions. The clonal evolutions included three cases of clones derived from the original ones seen at diagnosis, a case with a clone that was completely different than the original one, a case of a clone that was a progression from diploidy to pseudodiploidy, and a case with a shift in the modal chromosome number. Modal chromosome numbers increased in one case, decreased in two, and were unchanged in two. Clonal evolution was considered to be an indicator of poor prognosis in patients with acute lymphoblastic leukemia. (27 Refs) (In JPN)

10. CORRELATION OF KARYOTYPE WITH CLINICAL FEATURES IN ACUTE LYMPHOBLASTIC LEUKEMIA.

Kaneko Y, Rowley JD, Variakojis D, Chilcote RR, Check I, Sakurai M
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Cancer Res; 42(7):2918-2929 1982

We studied the clinical and karyotypic features of 50 patients with acute lymphoblastic leukemia, including 33 American and 17 Japanese patients, at two institutions. Clonal chromosome abnormalities were found in 39 of the 50 patients (78%) at diagnosis. Eleven patients had diploidy (N patients). Among the 39 aneuploid patients, 17 had pseudodiploidy (A1 patients), eight had hyperdiploidy with 47 to 49 chromosomes (A2 patients), nine had hyperdiploidy with 50 to 59 chromosomes (A3 patients), and five had other chromosome abnormalities. Of 14 patients whose chromosomes were also studied at relapse, eight had karyotypic progression, five had abnormalities identical or similar to those observed at diagnosis, and one had a change of karyotype from diploidy to aneuploidy. The median age and the median white blood cell count (WBC) of A3 patients were lower than those of any other group of patients, and all A3 patients had non-T-cell non-B-cell markers. The median age and the median WBC of A1 patients were higher than those of any other group of patients, although one-third of the patients had WBC below 20 x 10(3)/ul, and they often had leukemic cells of T-cell or B-cell lineage. The A2 patients were relatively old and tended to have higher WBC. The N patients were relatively young and tended to have low WBC, although these tendencies were not as marked as those in A3 patients. The A3 patients had longer survival times than the A1 ($p = 0.003$) or A2 (p = 0.002) patients. Also, N patients had longer survival times than A1 (p = 0.03) or A2 (p = 0.05) patients. The difference in survival times between A3 and N patients was not significant. Our study demonstrated that the karyotype is correlated with survival and with other recognized prognostic factors. However, in some A1 and A2 patients, the karyotype was a more reliable factor in indicating a poor prognosis than was the WBC or age. (Author abstract) (46 Refs)

11. NORMAL SISTER CHROMATID EXCHANGE FREQUENCY IN LONG-TERM SURVIVORS WITH ACUTE LEUKEMIA.

Inoue S, Brown L, Ravindranath Y, Ottenbreit MJ
Children's Hosp. Michigan, Detroit, MI, 48201
Cancer Res; 42(7):2906-2908 1982

We hypothesized that the sister chromatid exchanges assay in acute leukemia long-term survivors may detect: (a) long-term effects of combined chemo- and radiotherapy; and possibly (b) those individuals with inherently deficient DNA repair. Accordingly, we determined the sister chromatid exchanges frequency in 26 blood specimens from 24 acute leukemia long-term survivors (patients) and 14 blood specimens from 13 control subjects (controls). The patients consisted of 23 children with acute lymphocytic and one child with acute myelocytic leukemia. The median length of chemotherapy was 5 years. Eighteen of the 24 patients also received prophylactic fractional central nervous system irradiation for the first 3 years of treatment, and one patient received therapeutic irradiation to the central nervous system. The median off-therapy period at the time of study was 2.5 years with a range of 0 to 7.5 years. The controls consisted of the parents of the patients and laboratory personnel. A mean exchange score per cell was established for each specimen (25 to 30 cells/specimen were scored), and it ranged from 3.0 to 9.7 in the patients and from 3.0 to 11.5 in the controls. A mean +- S.D. calculated from those means was 6.0 +-1.8 for the patients and 6.9 +-2.8 for the controls. They were not significantly different. We conclude that chemo- and radiotherapy produced no persistent DNA alterations detectable by this method. (Author abstract) (20 Refs)

12. CYTOGENETIC STUDIES OF PERIPHERAL MYELOBLASTS AND BONE MARROW FIBROBLASTS IN ACUTE MYELOFIBROSIS.

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Am J Clin Pathol; 77(6):762-766 1982

Chromosome analysis with giemsa-trypsin banding was performed on circulating myeloblasts and cultured bone marrow fibroblasts from a patient with acute myelofibrosis. Major karyotypic abnormalities were found in the myeloblasts involving chromosomes number 1, 3, 5, 13, and 16; no chromosome abnormalities were detected in the fibroblasts. In addition, a pericentric inversion of number 7 was present in the circulating blasts but not the fibroblasts. Pericentric inversions have not previously been associated with acquired abnormalities of malignant cells. These findings support the concept that acute myelofibrosis is a primary malignancy of hematopoietic cells associated with secondary marrow fibrosis. The entity of acute myelofibrosis is discussed and the results of cytogenetic studies of previous reports are reviewed. (Author abstract) (28 Refs)

DNA CONTENT AND PLOIDY CHANGES ASSOCIATED WITH CANCER

13. PROGNOSTIC IMPLICATIONS OF PLOIDY AND PROLIFERATIVE ACTIVITY IN HUMAN SOLID TUMORS.

Barlogie B, Johnston DA, Smallwood L, Raber MN, Maddox AM, Latreille J, Swartzendruber DE, Drewinko B
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Cancer Genet Cytogenet; 6(1):17-28 1982

Ploidy and cell cycle compartment distribution were measured by DNA flow cytometry in 261 patients with a variety of tumors. Eighty-one percent of all tumors were aneuploid, and 72% were hyperdiploid. Ploidy levels spanned a wide range from hypodiploid to hyperoctaploid with mean and median values coinciding at a near-triploid DNA content. The proportion of cells with G1 DNA content decreased with increasing hyperdiploid abnormality. While unrelated to biopsy site and to a number of host factors such as age, sex and race, both ploidy and cytokinetic parameters were markedly affected by histopathologic diagnosis. Patients with metastatic lung, breast, and GI cancer had higher ploidy levels than individuals with the corresponding primary tumors. Ploidy remained constant, and G1/0 proportions showed only minor variation by disease site and over a median observation time of 6 mo. Prognostic factor analysis was performed in the subgroup of patients studied within 6 mo from diagnosis. The adverse impact of low tumor G1/0 proportion on survival was lost as the proportional hazard analysis was extended to include diagnostic subgroups. Accounting for histopathologic diagnosis, stage of disease, ploidy, and the proportion of tumor G1/0 cells, the following sequence of adverse prognostic factors in order of their relative ranks was established: absence of breast cancer, hypertriploid DNA index and presence of metastatic disease. Our study demonstrates that DNA content-derived information on intrinsic tumor cell features pertaining to cytogenetics and cytokinetics may provide an objective means of biologically relevant cancer classification. (25 Refs)

14. SEPARATION OF NORMAL AND LEUKEMIC LEUKOCYTES BY NEW DENSITY GRADIENT (DG) AND IDENTIFICATION BY FLOW CYTOMETRY (FC) (MEETING ABSTRACT).

Walle A, Espiritu E, Andreeff M
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Program and Abstracts of the 6th Annual Meeting of the Cell Kinetics Society, March 19-21, 1982, Houston, Texas. The Cell Kinetics Society 38 pp., 1982.

Cells with different surface immunoglobulin quantities (SIg+, SIg-), and with different DNA content (diploid, aneuploid) can be separated and enriched in specific fractions of a new DG. The DG consists of silica gel particles and has the highest resolution between 1.033 and 1.075 g/ml. In 6/9 untreated patients with acute leukemia (AL), and in 5/9 patients with AL and chronic myelogenous leukemia in blastic phase treated with chemotherapy, aneuploid cells (1.6C-2.4C, normal 2.0C) could be enriched in specific density layers to 96%. In all 17 patients no aneuploid cells were found by routine FC. In addition, mononuclear blood cell suspensions from normal donors could be enriched to 95% SIg+, and depleted to 96% SIg- cells in different layers of the same DG. (no Refs)

15. CYTOKINETIC ANALYSIS OF LEUKEMIC CELLS BY FEULGEN CYTOFLUOROMETRY COMBINED WITH 3H-THYMIDINE AUTORADIOGRAPHY.

Shimazaki C, Nakanishi S, Haruyama H, Isemura T, Nakagawa M, Ijichi H
Second Dept. Internal Medicine, Kyoto Prefectural Univ. Medicine, Kyoto, Japan
Nippon Ketsueki Gakkai Zasshi; 45(3):641-645 1982

Cytofluorometric data of leukemic cells from a patient with blastic crisis of chronic myelogenous leukemia revealed two different cell populations, 2C (probably derived from a Philadelphia' chromosome + clone) and 3C (probably derived from an anaplastic clone emerging during the blastic crisis). Shortest durations of the S phase of the 2C and 3C subpopulation were estimated to be 12 hr and 12.9 hr, respectively. Av duration of the S phase of the 2C subpopulation was estimated to be 20 hr. Cytofluorometry was useful to measure the absolute length of the S phase of the subpopulations by single sampling. (10 Refs) (In JPN)

16. MODAL VOLUMES AND DNA DISTRIBUTION OF LEUKEMIC LYMPHOMAS WITH SPECIAL CONSIDERATION TO TETRAPLOID CELLS (MEETING ABSTRACT).

Kusen R, Hausmann K, Schubbe H, Beck HP
Hamatologische Abteilung des Allgemeinen Krankenhause St Georg, Hamburg, W. Germany
Onkologie; 4(5):256 1981

Chronic B-lymphocyte leukemias and leukemic immunocytomas (115 in number) had modal volumes in the Coulter TF between 100 and 200 fl (max frequency: 140-150 fl; in the lymphocytes of control subjects: 165-180 fl). B-prolymphocytic leukemias (5 in number) were diploid with modal volumes between 164 and 318 fl. Tetraploid cells morphologically recognizable because of their dense nuclear structures and confirmed by flow cytometry (DNA content) were found in high grade malignancy in 1) preterminal transformation of 2 leukemic immunocytomas (1 x volume of 374 fl; 1 x doubled DNA content in 81% of the cells) and a B-prolymphocytic leukemia (volume 267 fl), 2) anaplastic centrocytomas (3 in number) with 34-54% of the peripheral cells having doubled DNA content and volumes above 300 fl which we designated as procentrocytes. On the other hand, a chronic lymphatic leukemia (CLL) diagnosed 2 yr previously and not in need of treatment whose cells had both B and T-cell markers at the same time showed 40% of its cells with doubled DNA content and a modal volume of 267 fl. (no Refs) (In GER)

17. FLOW CYTOMETRY OF LUNG CARCINOMA: A COMPARISON OF DNA STEMLINE AND CELL CYCLE DISTRIBUTION WITH HISTOLOGY.

Olszewski W, Darzynkiewicz Z, Claps ML, Melamed MR
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Anal Quant Cytol; 4(2):90-94 1982

The DNA distribution was obtained by flow cytometry of lung tumor cell suspensions from 32 carcinomas and 1 carcinoid. The former included 13 epidermoid carcinomas, 16 adenocarcinomas, 2 large-cell and 1 small-cell (oat-cell) undifferentiated carcinoma. Four tumor cell suspensions from grossly visible hilar lymph node metastases were also studied. The cancer cells made up 12-85% of the total cell populations obtained from the primary tumors and 10-66% of the cell suspensions from lymph node metastases. In all cases, the lung cancer cells showed single modal aneuploid levels of DNA, ranging from 2.15c to 5.05c. DNA levels in epidermoid carcinomas were slightly less than those of adenocarcinomas. No difference in ploidy was observed between cells in lymph node metastases and those of the corresponding primary tumor. Malignant and benign cells were differentiated on the basis of hyperploidy of lung cancer cells in GOG1 populations. For the 32 carcinomas as a group, approx 25% of the tumor cells were in S phase and 10% in G2M phase, although there was considerable variation from case to case. Epidermoid carcinomas had a greater proportion of cells in the so-called proliferative pool (S + G2 + M) than did adenocarcinomas. The single carcinoid case exhibited very few cells in proliferative phases. The elevated values of DNA in G0G1 cells may be a highly reliable marker for carcinoma of the lung and could be the basis for cytological diagnosis instrumentation if appropriate, representative samples can be obtained. (20 Refs)

18. DNA CONTENT AS A MARKER OF PRE-CANCEROUS LESIONS OF THE DIGESTIVE TRACT (MEETING ABSTRACT).

Capurso L, Teodori L, DeVita R, Galloni L, Tarquini M, Mauro F, Nervi C, Pallone F
Cattedra Gastroenterologia Universita, Rome, Italy
Gastroenterology; 82(5,part2):1029 1982

In order to detect the abnormality of the DNA content distribution as a marker of precancerous or early cancerous lesions of the digestive tract, human endoscopic biopsies have been analyzed. Samples were derived from stomach, duodenum and colon of normal donors and of patients clinically classified as affected by non-neoplastic lesions such as ulcer, atrophic gastritis, chronic gastritis and polyps. Sample processing has been performed by mechanical and enzymatic treatment (collagenase and haluronidase vs pepsin treatment revealed no significant changes in the DNA pattern). Staining for flow cytometric analysis (Phywe Ortho ICP 22) has been achieved by ethidium bromide and mithramycin. Normal samples exhibited the usual DNA distribution with G1/0,S and G2/M compartments. An aneuploid cell subpopulation was found in 4/7 atrophic or chronic gastritis specimens. Such aneuploidy is similar to that typical of gastric adenocarcinoma, DNA index ranging from 1.1 to 1.4 in comparison to 1.0. However, the percent aneuploid cells in the majority of tumors was generally higher than in aneuploid gastrites. Furthermore, polyps also exhibited an aneuploid peak, while ulcers were characterized by a normal, diploid DNA content. It is likely that the occurrence of aneuploidy in non-neoplastic lesions reflects some pre-cancerous situation or the presence of an early, small fraction of neoplastic cells. (no Refs)

19. ADENOCARCINOMA AND MIXED CARCINOMA OF THE UTERINE CERVIX. II. PROGNOSTIC VALUE OF NUCLEAR DNA ANALYSIS.

Fu YS, Reagan JW, Fu AS, Janiga KE
Inst. Pathology, Case Western Reserve Univ., Cleveland, OH, 44106
Cancer; 49(12):2571-2577 1982

The prognosis of the glandular neoplasms of the uterine cervix is related to the clinical stage and, to a lesser extent, to the histologic type, growth pattern, and degree of differentiation of the neoplasms. To determine further the prognostic significance of the stem cell ploidy levels as determined by nuclear DNA quantitation, the authors separated the tumors into low ploidy (less than 3N) and high ploidy (greater than 3N) groups. Of the clinical Stage I and II neoplasms, low ploidy tumors had a better prognosis than high ploidy tumors of comparable stage. Low ploidy tumors had a better prognosis than high ploidy tumors irrespective of the degree of differentiation. Mixed carcinomas had a poorer prognosis than pure adenocarcinomas of comparable clinical stage. This might be explained by the greater proportion of high ploidy stem cells in mixed carcinomas than in pure adenocarcinomas. Although advanced clinical Stage III and IV neoplasms had a poor outlook regardless of the DNA ploidy level, there was a proportional increase of high ploidy tumors with increasing clinical stage. These findings suggest that cervical glandular neoplasms having high ploidy stem cell lines are biologically more aggressive than those with low ploidy stem cell lines. (Author abstract) (9 Refs)

20. S AND G-2 TRANSIT IN RELATION TO DNA PLOIDY IN MIXED, POLYPLOID TUMOR POPULATIONS (MEETING ABSTRACT).

Sklarew RJ, Post J
University Medical Center, Goldwater Memorial Hospital, Roosevelt Island, NY, 10044
Program and Abstracts of the 6th Annual Meeting of the Cell Kinetics Society, March 19-21, 1982, Houston, Texas. The Cell Kinetics Society 38 pp., 1982.

Polyploid MCA rat sarcoma cultures were pulse-labelled with 3H-TdR (thymidine), grown in Colcemid for intervals of up to 18 hrs, and pulse-labeled with 14-CTdR prior to fixation. In autoradiographs the Feulgen DNA content and grain count were determined for G-2 and mitotic cells labeled with 3H-alone. A Quantimet 720 imaging system was used to automate the simultaneous measurements. The serial DNA distributions and labeling indices of 3H-labeled G-2 and mitotic cells suggested that 1) S-transit is prolonged with increasing DNA ploidy level over a four-fold ploidy range; 2) higher DNA ploidy is also associated with prolongation of G-2 transit; 3) subpopulations of higher DNA ploidy tend to leave the cycle in G-2 as cultures reach confluency; 4) whereas, co-existent diploid cells leave the cycle in G-1; 5) decreased S-transit (with increasing ploidy) is associated with lower average rates of DNA synthesis, as determined by mean 3H-TdR grain counts. (1 Ref)

CHROMOSOMAL FRAGILITY AND GENETIC FACTORS PREDISPOSING TO HUMAN CANCER

21. FAMILIAL MELANOMA ASSOCIATED WITH DOMINANT ULTRAVIOLET RADIATION SENSITIVITY.

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Cancer Res; 42(7):2909-2912 1982

Sensitivity to ultraviolet radiation was studied in lymphoblastoid cell lines derived from 32 members of two families with histories of multiple primary melanomas in several generations. As assayed by colony formation in agar or by trypan blue exclusion following irradiation, cellular sensitivity showed a bimodal distribution. All persons with melanoma or multiple moles were in the sensitive group, while some family members exhibited responses similar to those of controls. Cells from four cases of sporadic melanoma showed normal levels of sensitivity. The data are consistent with a dominantly inherited ultraviolet light sensitivity associated with these examples of familial melanoma. Spontaneous and ultraviolet light-induced sister chromatid exchange frequencies were similar to those in control cell lines. No defect in excision repair was detected in any of the above cell lines, but the sensitive group showed postirradiation inhibition of DNA replication intermediate between controls and an excision-deficient xeroderma pigmentosum cell line. (Author abstract) (25 Refs)

22. ABNORMALITIES OF CHROMOSOME 13 IN RETINOBLASTOMAS FROM INDIVIDUALS WITH NORMAL CONSTITUTIONAL KARYOTYPES.

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Cancer Genet Cytogenet; 6(3):213-221 1982

Constitutional chromsome abnormalities have been associated with retinoblastoma, Wilms' tumor, and a familial form of renal cell carcinoma. For each tumor type, the particular chromosome segment involved in the observed rearrangements is different: in retinoblastoma, that segment is band q14 on chromosome 13. We now present evidence that in retinoblastoma, structural abnormalities involving the particular chromosome segment identified in the constitutional cases can also occur in the tumors of individuals with normal constitutional karyotypes. Six cases with retinoblastomas in one or both eyes were analyzed; deletions/ rearrangements involving 13q14 were found in the tumor cell karyotypes of five of the six. These observations suggest that changes in a gene or genes at a common site (13q14) play a role in tumorigenesis in all forms of retinoblastoma, sporadic as well as heritable. (Author abstract) (22 Refs)

23. MULTIPLE KARYOTYPIC CHANGES IN RETINOBLASTOMA TUMOR CELLS: PRESENCE OF NORMAL CHROMOSOME NO. 13 IN MOST TUMORS.

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Cancer Genet Cytogenet; 6(3):201-211 1982

There are conflicting reports on the frequency in retinoblastoma tumor cells of aberrations involving chromosome No 13. To quantitate the frequency of various chromosome aberrations, we analyzed the karyotypes from 10 retinoblastoma tumors; all tumors contained chromosome abnormalities. Chromosome No 13 was altered in only two tumors, but the aberrations in these two cases affected different portions of the chromosome. We have concluded that chromosome aberrations affecting chromosome No 13 are relatively infrequent in retinoblastoma tumors. Chromosome No 1 was involved in rearrangements in eight tumors; in six tumors the rearrangements lead to trisomy of 1q25-1q32. Seven tumors had aberrations resulting in trisomy of the long arm of chromosome No 17; the most common aberration was an i(17q) chromosome. Every tumor showed trisomy of the long arm of either chromosome No 1 or 17. These changes in chromosomes No 1 and 17 have been observed by others in many different tumors and are not unique to retinoblastoma. In summary, chromosome abnormalities were present in all retinoblastoma tumors studied, but no aberration common to all tumors was found. (Author abstract) (21 Refs)

24. RETINOBLASTOMA AND ITS ASSOCIATION WITH A DELETION IN CHROMOSOME NUMBER 13: A SURVEY USING HIGH-RESOLUTION CHROMOSOME TECHNIQUES.

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Cancer Genet Cytogenet; 6(1):29-37 1982

To our knowledge. 20 cases of retinoblastoma associated with a chromosome number 13 aberration have been reported. The present study utilized high-resolution prophase banding analysis of 12 additional retinoblastoma patients to determine the occurrence of chromosome aberrations and identify consistently associated clinical abnormalities. Six male and six female patients were studied representing seven cases of bilateral and five cases of unilateral retinoblastoma. One case of unilateral and two cases of bilateral retinoblastoma had detectable cytogenetic abnormalities, all involving an interstitial deletion of 13q14 on the long arm of one chromosome number 13. In all five unilateral cases the tumor manifested in the left orbit, and in all seven bilateral cases the left eye was at a more malignantly advanced stage than the right eye. All three cases with a chromosome abnormality had varying degrees of developmental and/or mental retardation, along with at least one other congenital abnormality. In addition to the 12 cases of retinoblastoma, a patient with severe ophthalmologic abnormalities and mild congenital anomalies was studied by the prophase banding technique and found to be partially trisomic for the q13-14 banding regions of chromosome number 13. These results further confirm the association of the 13q14 region with gene loci for optic development and indicate that cytogenetic abnormalities may occur even more frequently in retinoblastoma than indicated by the small number of cases reported in the literature. (Author abstract) (34 Refs)

25. FAMILY STUDIES ON THE CHROMOSOMAL LOCATION OF THE RETINOBLASTOMA GENE (RB-1).

Morten JE, Harnden DG, Bundey S
MRC Clinical and Population Cytogenetics Unit, Western General Hosp., Edinburgh EH4 2XU, Scotland
J Med Genet; 19(2):120-124 1982

The segregation of chromosomes 13 distinguishable by Q band fluorescent polymorphisms has been studied in three families with retinoblastoma. The recombination fraction for two of these families and four families previously reported did not differ significantly from 50%. Since a high recombination fraction has been predicted from chiasma frequency between the centromere of chromosome 13 and 13q14 these results neither confirm nor refute the location of the autosomal dominant gene predisposing to retinoblastoma in 13q14. The use of fluorescent markers is not suitable for early recognition of gene carriers in families with retinoblastoma. (Author abstract) (14 Refs)

26. CHIASMA DERIVED GENETIC MAPS AND RECOMBINATION FRACTIONS: CHROMOSOME 13 WITH REFERENCE TO THE PROPOSED 13Q14 RETINOBLASTOMA LOCUS.

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J Med Genet; 19(2):125-129 1982

Provided that there is no chromatid interference, no movement of chiasmata, and no discrepancies between meiotic and mitotic chromosome lengths, then genetic maps and recombination fractions may be directly derived from our meiotic chiasma distribution data. This is illustrated by male chiasma derived genetic lengths and recombination fractions along chromosome 13. The recombination fraction between 13p fluorescent markers and the proposed retinoblastoma locus at 13q14 is estimated at 0.27 to 0.37 and preliminary female chiasma studies suggest a recombination fraction of 0.5 between these two sites. Therefore, it seems unlikely that 13p fluorescent markers may be of any practical help in identifying retinoblastoma gene carriers. This is also borne out by the discordant segregation which has been found in six out of seven retinoblastoma families, which gives a calculated recombination fraction of 0.39 (SE 0.15), not significantly different form 0.5. (Author abstract) (17 Refs)

27. UV-REPAIR IS IMPAIRED IN FIBROBLASTS FROM PATIENTS WITH FANCONI'S ANEMIA.

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MGG; 185(3):454-456 1982

Fanconi's anemia, a hereditary autosomal disease with chromosomal instability, elevated incidence of cancer and clinical symptoms is accompanied by a DNA repair deficiency. Fibroblasts from patients with Fanconi's anemia were found to be impaired in the DNA repair of UV damage. Nucleoid decondensation and recondensation after UV irradiation were less efficient in fibroblasts from patients with Fanconi's anemia than in those from a healthy proband. These data confirm our earlier findings that DNA ligase is deficient in Fanconi's anemia. (Author abstract) (12 Refs)

28. ACUTE MYELOID LEUKEMIA AS THE FIRST HEMATOLOGIC MANIFESTATION OF FANCONI ANEMIA.

Auerbach AD, Weiner MA, Warburton D, Yeboa K, Lu L, Broxmeyer HE
Lab. Investigative Dermatology, Rockefeller Univ., 1230 York Ave., New York, NY, 10021
Am J Hematol; 12(3):289-300 1982

A 6-yr-old girl with Fanconi anemia (FA) developed acute myeloid leukemia (AML) as the first hematologic manifestation of the syndrome. She remains in remission 18 mo after diagnosis although her management is complicated by unusual sensitivity to chemotherapeutic agents. Marrow cells studied prior to initiation of leukemia therapy showed increased chromosome breakage and an abnormal clone in which a number 7 and a number 8 chromosome were replaced by two marker chromosomes. During the present remission her cultured lymphocytes, bone marrow cells, and fibroblasts showed increased 'spontaneous' chromosome breakage as well as enhanced sensitivity to the clastogenic effect of the difunctional alkylating agent diepoxybutane (DEB), features characteristic of FA. Eight mo into remission 50% of her marrow cells comprised an abnormal clone, which was monosomic for the number 7 chromosome but had both copies of number 8; in addition a variable number of unique marker chromosomes were present in clonal as well as nonclonal cells. This same marrow sample, upon culture, showed an abnormal growth pattern of CFU-GM, absence of detectable CFU-GEMM and BFUe, non-responsiveness of CFU-GM to inhibition by acidic isoferritins, increased bone marrow acidic isoferritin inhibitory activity, and absence of detectable bone marrow cell-derived GM-CSF. The

implications of these findings to leukemogenesis in FA are discussed. (Author abstract) (40 Refs)

29. SCE IN BLOOM SYNDROME B AND T LYMPHOCYTES.

Block AM, Shiraishi Y, Sandberg AA
(c/o Sandberg), Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Clin Genet; 21(3):184-186 1982

Sister chromatid exchange (SCE) levels were studied in mixed lymphocyte populations from five patients with Bloom's disease. When cells were treated with mitogens that stimulated T and B cells, no significant differences in SCE were noted between the two populations. Gaps, ring chromosomes and quadriradials were noted; double minutes were noted in lipopolysaccharide-stimulated cultures in one patient. (7 Refs)

30. 'WASTED,' A NEW MUTANT OF THE MOUSE WITH ABNORMALITIES CHARACTERISTIC OF ATAXIA TELANGIECTASIA.

Shultz LD, Sweet HO, Davisson MT, Coman DR
Jackson Lab., Bar Harbour, ME, 04609
Nature; 297(5865):402-404 1982

Pathological changes similar to those of ataxia telangiectasia, found in the CNS and lymphoid system of mutant mice (HRS/J mice backcrossed to C57BL/6J mice), are described. Homozygosity for the wasted mutation results in impaired neurological and immunological development, as well as increased levels of spontaneous and gamma ray-induced chromosomal damage. The relationship of the chromosomal aberrations to defective DNA repair is discussed. (11 Refs)

31. ORGAN SITE SPECIFICITY FOR CANCER IN CHROMOSOMAL INSTABILITY DISORDERS.

Feinberg AP, Coffey DS
(c/o Coffey) Oncology Center, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Cancer Res; 42(8):3252-3254 1982

DNA rearrangement rather than point mutation is an emerging hypothesis for human carcinogenesis. Although there is no direct evidence for this hypothesis, indirect evidence is provided by cancer cytogenetics and genetics. It has been suggested that patients with Bloom's syndrome, a disorder of spontaneous chromosomal rearrangement, develop the common fatal internal cancers and thus that genetic rearrangements, rather than chemical mutagens, cause most internal human cancers. To test this observation, we have derived age- and sex-adjusted cancer incidence rate ratios for specific organ sites in patients with three chromosomal instability disorders (Bloom's syndrome, xeroderma pigmentosum, and dyskeratosis congenita) and have found that the increased incidence of cancer in all three disorders limited to specific and often uncommon organ sites. We conclude that chromosomal instability disorders do not predispose patients to the common fatal internal cancers. Although DNA rearrangement remains a promising concept in human carcinogenesis, the organ site specificity of cancers associated with Bloom's syndrome, xeroderma pigmentosum, and dyskeratosis congenita cannot be used as evidence to implicate this mechanism. (Author abstract) (37 Refs)

CHROMOSOMES OF HUMAN CELL LINES AND TUMORS IN VITRO

32. ESTABLISHMENT AND CHARACTERIZATION OF TWO NEOPLASTIC CELL LINES (U-1285 AND U-1568) DERIVED FROM SMALL CELL CARCINOMA OF THE LUNG.

Bergh J, Larsson E, Zech L, Nilsson K
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Acta Pathol Microbiol Scand [A]; 90(3):149-158 1982

Two human cell lines have been established in vitro from patients with small cell carcinoma of the lung (SCC). The U-1285 line was derived from the classical small cell type of SCC while the U-1568 originated from a larger cell variant. The cell lines grow as suspension cultures and have been passaged continuously in vitro for 3 yr (U-1285) and 2 yr (U-1568), respectively. The malignant nature of the lines is suggested by their infinite growth potential, their capacity to form colonies in agarose and their aneuploidy. Both cell lines contain cytoplasmic electron dense particles indistinguishable from classical neurosecretory granules but only in U-1568 has hormone production (human chorion gonadotropin (alpha-HCG)) been proven. The U-1568 line produces carcino-embryonic antigen (CEA) while both U-1285 and U-1568 produce alpha-feto-protein (AFP). Chromosome analysis reveal aneuploidy of both lines. Among structural aberrations, involvement of chromosome 14 in U-1285 and chromosomes 1, 7 and 12 in U-1568 is interesting since alterations of these chromosomes have been described previously in other malignant conditions. (Author abstract) (44 Refs)

33. A NONRANDOM CHROMOSOMAL ABNORMALITY, DEL 3P(14-23), IN HUMAN SMALL CELL LUNG CANCER (SCLC).

Whang-Peng J, Bunn PA, Kao-Shan CS, Lee EC, Carney DN, Gazdar A, Minna JD
NIH, Building 10, 12N 226, Bethesda, MD, 20205
Cancer Genet Cytogenet; 6(2):119-134 1982

In order to determine whether or not there are specific chromosomal changes in small cell lung cancer (SCLC), karyotypic analyses of 16 continuous SCLC tissue culture lines, three fresh tumor specimens (bone marrow), one direct preparation of bone marrow involved with SCLC, and two lymphoblastoid lines derived from SCLC patients were studied. Cell lines were derived from primary tumor, or metastases to bone marrow, subcutaneous nodules, or pleural fluid; all 16 lines had biochemical and histologic properties characteristic of SCLC. Of the 15 males and 3 females, 6 patients had no prior treatment. All of the 16 cell lines, the 3 fresh specimens, and the direct bone marrow preparation had a common deletion of the short arm of chromosome number 3. Use of the shortest region of overlap analysis showed the common deletion was of the short arm in the regions p(14-23). This specific chromosomal abnormality, del 3p, was not found in five non-SCLC cell lines studied and is of major potential biological and diagnostic importance. (Author abstract) (29 Refs)

34. ESTABLISHMENT AND CHARACTERIZATION OF A HUMAN MYELOMA CELL LINE (KMM-1).

Togawa A, Inoue N, Shimoda M, Mannoji M, Yawata Y, Miyamoto K, Namba M
Dept. Internal Medicine, Kawasaki Medical Sch., Kawasaki, Japan
Nippon Ketsueki Gakkai Zasshi; 45(3):607-614 1982

A new cell line (KMM-1) was established from an sc plasmacytoma from a 62-yr-old man with multiple myeloma. The cells, serially cultured in suspension for 60 generations, have a doubling time of 36-40 hr. The cells have a karyotype of 47, X, -Y, 1q+,-2, +t(1:2) (cen:cen), +7, 12q+, 14q+, + mar. and have no Epstein-Barr virus determined nuclear antigen. Characteristics of other myeloma cell lines are compared with those of KMM-1. (25 Refs) (In JPN)

35. ESTABLISHMENT AND CHARACTERIZATION OF TWO HUMAN PANCREATIC CANCER CELL LINES TUMORIGENIC IN ATHYMIC MICE.

Dexter DL, Matook GM, Meitner PA, Bogaars HA, Jolly GA, Turner MD, Calabresi P
Dept. Medicine, Roger Williams General Hosp., 325 Chalkstone Ave., Providence, RI, 02908
Cancer Res; 42(7):2705-2714 1982

Two human pancreatic cancer lines, RWP-1 and RWP-2, have been established from two patients with primary pancreatic cancer metastatic to the liver. The patients' tumors, the xenografted tumors, and tumors obtained by inoculation of nude mice with cultured RWP-1 and RWP-2 cells are all moderately-well-differentiated ductal cell adenocarcinomas. Ultrastructural analysis supports the tissue histopathology findings. Xenografts of RWP-1 tumors double every 10 days, whereas the doubling time of RWP-2 xenografts is 22 days. Both tumors contain mucin. RWP-1 and RWP-2 cells have a doubling time in culture of 45 hr and form colonies in soft agar. RWP-1 cultures appear to be morphologically heterogenous; two distinct epithelial cell types can be identified. RWP-1 and RWP-2 have modal chromosome numbers of 64 and 62, respectively. Appreciable levels of glucose-6-phosphate dehydrogenase and lactic dehydrogenase were found in both cell lines and xenografts. RWP-1 and RWP-2 cells produce appreciable amounts of carcinoembryonic antigen, 1,090 and 414 ng/10(6) cells, respectively. (Author abstract) (51 Refs)

36. KARYOTYPE CONSISTENCY IN HUMAN COLORECTAL CARCINOMA CELL LINES ESTABLISHED IN VITRO.

Chen TR, Hay RJ, Macy ML
American Tissue Culture Collection, 12301 Parklawn Dr., Rockville, MD, 20852
Cancer Genet Cytogenet; 6(2):93-117 1982

Karyotypes of nine human colorectal cell lines deposited with the ATCC were studied by trypsin-Giemsa banding. CCL 229,230,231 and 235 belong in the stable type that is characterized by karyotypes consisting mostly of normal chromosomes and stable markers. CCL 228, 234, and 238 being in the unstable type that has karyotypes consisting of numerous markers in addition to normal chromosomes and stable markers. The remaining intermediate type has karyotypic characteristics between the above two types usually with two or less unstable markers per cell. The stable markers (together with normal chromosomes) are constitutive components of a cell genome and are common to most cells within the same cultured population. Unstable markers are the likely cause of karyotypic variations between cells and often are produced by balanced inter- and intrachromosome changes, or both. Consequently, total chromosome length per cell genome is remarkably consistent within a cell population, and karyotypes between cells are profoundly stable and mostly identical. Chromosome deletions and interhomologue exchanges had the highest incidences among both stable and unstable markers. The complex markers occurred relatively infrequently. There were neither common markers nor unique chromosome breakages common to all of these established cell lines. The significance of chromosome changes involving No 7 in this as well as other tumor pathotypes is briefly discussed. (35 Refs)

37. MALIGNANT TRANSFORMATION OF HUMAN EMBRYO RETINOBLASTS BY CLONED ADENOVIRUS 12 DNA.

Byrd P, Brown KW, Gallimore PH
Cancer Res. Campaign Laboratories, Dept. Cancer Studies, Medical Sch., Univ. Birmingham, Birmingham B15 2TJ, England
Nature; 298(5869):69-71 1982

Isolation of a recombinant plasmid (pAsc2)-trans human embryo retinoblast (HER) cell line that contains many copies of the adenovirus Type 12 (Ad 12) transforming region, expresses virus-specified proteins, and following inoculation into athymic mice, forms tumors which resemble retinoblastomas is described. Primary cultures of human retinoblasts were transfected with pAsc2, and one transformed focus, identified 45 days after transfection, was isolated and established as a continuous cell line. The cell line has been designated Ad 12 HER1 and was the first reported Ad 12-transformed human cell line. Cytogenetic analysis revealed a pseudotetraploid human karyotype. The Ad 12 HER1 cell line was grown beyond the thirty-sixth tissue culture passage level and at no time has its growth entered a crisis phase. When Ad 12 HER1 cell DNA was digested with the restriction endonucleases BglII or SstI and subjected to Southern blotting analysis using P-labeled Ad 12 EcoRI-C DNA fragments as a probe, Ad 12 sequences were found on many DNA fragments whose sizes ranged from greater than 12 kilobase pairs (kb) to 2.2 kb. As these enzymes cleave host DNA sequences only, each fragment represented a separate insert of pAsc2 sequences. Results suggested that Ad 12 HER1 cells contain intact, integrated copies of viral and vector sequences and it is likely that some of the inserts contain tandem repeats of the entire recombinant plasmid. Histological analysis of the Ad 12 HER1-induced tumors showed them to consist of clusters of small cells with many mitotic figures characteristic of poorly differentiated human retinoblastomas. (29 Refs)

38. IN VITRO SELECTION OF FRESHLY RESECTED GLIOMA CELL POPULATIONS (MEETING ABSTRACT).

Rankin-Shapiro J, Shapiro WR
Memorial Sloan-Kettering, New York, NY, 10021
In Vitro; 18(3,part2):284 1982

We investigated selection among clonal subpopulations from heterogeneous malignant brain tumors. Fifty-five clones, identified by karyotype as clonal subpopulations of 5 freshly resected human gliomas, were studied from the time of their initial plating through 12 serial passages. By passage 12 the heterogenous parental lines contained no metaphases representative of the original tumor, although known marker chromosomes were present in some of the karyotypes. During in vitro passaging of the clones, two distinct stability patterns emerged; clones that retained their parental karyotypic deviation (stable phenotype) and clones that gave rise to new variant cells (unstable phenotype). Analysis of the karyotypic deviations revealed that the changes involved the frequent gain or loss of whole chromosomes but only rare structural changes. Cells that demonstrated the unstable phenotype were more likely to be hyperploid than were stable cells; a gain or loss of chromosome 21 was associated with instablity irrespective of ploidy, while a loss of chromosome 13 occurred in 7 of 9 near-diploid cells that were unstable. During serial passage, chromosomes 1, 3, 9, 22 and X were lost while chromosomes 19, 20 and 21 were gained. Recloning each parental line demonstrated that many of the variant cells generated had a selective growth advantage greater than the parental cell. (no Refs)

39. CLONAL ORIGIN OF THE PHILADELPHIA TRANSLOCATION IN CHRONIC MYELOID LEUKEMIA DEMONSTRATED IN SOMATIC CELL HYBRIDS USING AN ADENYLATE KINASE-1 POLYMORPHISM.

Geurts van Kessel AH, Van Agthoven AJ, Hagemeijer A

Dept. Cell Biology and Genetics, Erasmus Univ., P.O. Box 1738, 3000 DR Rotterdam, The Netherlands

Cancer Genet Cytogenet; 6(1):55-58 1982

Hybrid cell lines were derived from fusion of rodent cells with leukocytes from a t(9q+; 22q-)-positive chronic myeloid leukemia (CML) patient carrying a chromosome No 9-linked adenylate kinase-1 (AK1) polymorphism (AK1 1-2). The AK1*2 allele was consistently expressed when 9q+ was present, whereas the AK1*1-coded isozyme was formed when the normal chromosome No 9 was present. These results provide additional data confirming the clonal origin of the Ph1 translocation in CML. (Author abstract) (13 Refs)

40. HUMAN LYMPHOMA-LYMPHOMA HYBRIDS AND LYMPHOMA-LEUKEMIA HYBRIDS. I. ISOLATION, CHARACTERIZATION, CELL SURFACE MARKERS, AND B-CELL MARKERS.

Zeuthen J, Klein G, Ber R, Masucci G, Bisballe S, Povey S, Terasaki P, Ralph P

Inst. Human Genetics, Univ. Aarhus, The Bartholin Building, DK-8000 Aarhus C, Denmark

JNCI; 68(2):179-195 1982

Four new somatic cell hybrids were obtained by fusion of various Burkitt's lymphoma (BL)-derived cell lines that had different selective markers: Raji-P3HR-1, Daudi-Raji, and a P3HR-1-P3HR-1 'autohybrid' derived from two P3HR-1 sublines. In addition, a hybrid was was obtained between the Daudi (BL) line and the human leukemia cell line K562. The hybrids were extensively characterized by means of chromosome, isozyme, and HLA surface markers. The phenotypic differences between the parent cell lines allowed some conclusions with respect to the expression of latent Epstein-Barr virus (EBV) genomes, C3 and EBV receptors, and of immunoglobulin and beta 2-microglobulin-HLA expression as well as the influence of the leukemia cell (K562) genome on B-cell properties in the Daudi-K562 hybrid. B-cell and differentiated markers of these hybrids were characterized. High-level expression dominated for the markers C3 and EBV receptors, which showed a good correlation coefficient of 0.84, as was true for Fc receptors and surface immunoglobulin. The Daudi-K562 hybrid showed loss of all B-cell markers but retention of the leukemia cell markers (eg, hemoglobin synthesis). (Author abstract) (59 Refs)

CHROMOSOMES OF ANIMAL CELL LINES AND TUMORS

41. IN VITRO CHARACTERIZATION OF FOUR N-[4-(5-NITRO-2-FURYL)-2-THIAZOLYL] FORMAMIDE (FANFT) INDUCED MOUSE BLADDER TUMORS.

Mickey DD, Mickey GH, Murphy WM, Niell HB, Soloway MS

Dept. Urology, Univ. Tennessee, Center Health Sciences, 956 Cour Ave., Box 10, Memphis, TN, 38163

J Urol; 127(6):1233-1237 1982

Four long-term murine bladder tumor cell lines were established in vitro. The four lines were initiated from primary N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (FANFT)-induced murine bladder tumors arising in C3H/He mice. Each was maintained as a solid tumor in syngeneic mice for at least 30 generations before initiation in tissue culture. The cell lines MBT-2, MBT-8, MBT-409, and MBT-683, have been subcultured over 75x in vitro for 18 mo. They are all epithelial, grow in islands on plastic Petri dishes before confluent growth and form colonies in soft agar suspension culture. Morphologic studies indicate that all four lines have epithelial characteristics and karyotypic studies indicate that all lines have polyploidy and marker chromosomes. Population doubling times range from 10 to 26 hr and are consistent for each line. (Author abstract) (27 Refs)

42. CYTOGENETIC CHARACTERIZATION OF MOUSE MYELOMA CELL LINES USED FOR PRODUCTION FOR HYBRIDOMAS (MEETING ABSTRACT).

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In Vitro; 18(3,part2):296 1982

In 1975 Kohler and Milstein reported the production of monospecific antibodies by fusing mouse spleen cells and cells from a murine continuous myeloma line. The resulting hybrid cells secreted monoclonal antibody into the cell culture medium. Because of the distinct advantages of monospecific antibodies over heterologous antibodies for immunological studies, this new hybridoma technology has resulted in an explosion of reports. It is important for quality control in research to characterize cell lines, particularly continuous cell lines, because of their property of immortality. The myeloma cell line originally used by Kohler and Milstein is designated P3/X63-Ag8, and it secretes immunologlobulins. The resulting hybridomas secrete mixtures of light and heavy immunoglobulin chains of both parental cells. Therefore, several clones were selected from the P3 parental line. The clone designated NS-1 secretes only kappa light chain; whereas clone 653, a second line, does not secrete any immunoglobulins. In addition, a third line, SP2/0, is frequently used for fusion. I have been analyzing these mouse myeloma cell lines by C-banding and nucleolar organizer region (NOR) techniques to identify marker chromosomes. Using these characterization studies, I identified contamination of one myeloma parental cell line by a hybridoma line. (no Refs)

43. IN VIVO SISTER CHROMATID EXCHANGE AND CELLULAR REPLICATION KINETICS OF NORMAL AND LYMPHOMA AKR BONE MARROW CELLS.

Biegel JA, Boggs SS, Conner MK
Univ. Pittsburgh Sch. Medicine, RC510 Scaife Hall, Pittsburgh, PA, 15261
Cancer Res; 42(7):2813-2815 1982

The recent development of an AKR(Rb6.15)1Ald lymphoma model in our laboratory presents a unique means of comparing sister chromatid exchange (SCE) frequencies and cellular replication kinetics of normal and lymphoma cells in the same host environment. Lymphoma cells, distinguished from normal cells by the presence of two metacentric chromosomes, had an average cell cycle time of 8 hr compared to 11 hr for normal cells. Normal bone marrow cells from nonleukemic AKR/J, nonleukemic AKR(Rb6.15)1A1d, and tumor passage recipients had similar base-line and 1,3-bis(2-chloroethyl)-1-nitrosourea-induced SCE frequencies following exposure to 4.4 mg 1,3-bis(2-chloroethyl)-1-nitrosourea per ml and 19 hr 5-bromo-2-deoxyuridine. While base-line SCE frequencies were only slightly higher, 1,3-bis(2-chloroethyl)-1-nitrosourea-induced lymphoma cell SCE frequencies were 3x higher than normal induced SCE frequencies [34.06 +-6.6 (SE) versus 11.0 +-0.6 SCEs/cell]. (Author abstract) (11 Refs)

GENE MAPPING STUDIES

44. UNIQUE FEATURES OF RETROVIRUS EXPRESSION IN F/ST MICE.

Morse HC, Kozak CA, Yetter RA, Hartley JW
Lab. Microbial Immunity, Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Disease, Bethesda, MD, 20205
J Virol; 43(1):1-7 1982

F/St mice are unique in producing high levels of both ecotropic and xenotropic murine leukemia virus. The high ecotropic virus phenotype is determined by three or more V (virus-inducing) loci. A single locus for inducibility of xenotropic murine leukemia virus was mapped to chromosome 1 close to, but possibly not allelic to, Bxv-1. Although the high ecotropic virus phenotype is phenotypically dominant, the high xenotropic virus phenotype was recessive in all crosses tested. Suppression of xenotropic murine leukemia virus is governed by a single gene which is not linked to the xenotropic V locus. (Author abstract) (18 Refs)

45. CYTOGENETIC MAPPING OF THE DUPLICATED SEGMENT OF CHROMOSOME 12 IN LYMPHOPROLIFERATIVE DISORDERS.

Gahrton G, Robert KH, Friberg K, Juliusson G, Biberfeld P, Zech L
Section Clinical Hematology and Oncology, Dept. Medicine, Huddinge Hosp., S-14186 Huddinge, Sweden
Nature; 297(5866):513-514 1982

Cytogenetic studies performed on peripheral blood lymphocytes, bone marrow cells, and spleen cells from a 56-yr-old man with lymphocytic non-Hodgkin's lymphoma indicated that the essential genes duplicated during leukemogenesis that leads to lymphoproliferative B-cell disorders characterized by trisomy of chromosome 12 are probably located on the segment q13 to q22. (10 Refs)

MOLECULAR CYTOGENETICS

46. CYTOGENETIC STUDIES ON THE NUCLEOLAR ORGANIZER REGION (NOR) ACTIVITY IN MENINGIOMA CELLS WITH NORMAL AND HYPODIPLOID KARYOTYPES.

Zankl H, Huwer H, Zang KD
Div. Human Biology and Human Genetics, Univ. Kaiserslautern, Pfaffenbergstrasse, 6750 Kaiserslautern, W. Germany
Cancer Genet Cytogenet; 6(1):47-53 1982

The association pattern and NOR silver staining of the acrocentric chromosomes was studied in normal and hypodiploid cell lines of four meningioma patients. In three cases the hypodiploid cells showed a more increased association frequency or NOR silver staining or both than the normal ones, indicating a compensatory mechanism between the NORs. Chromosomes number 14 seemed to be more frequently involved in this phenomenon than other acrocentric chromosomes. From the silver staining results it was concluded that in meningioma cells, chromosomes number 22 which bear active as well as inactive NORs were missing. The compensation between the NORs was probably only activated if an active NOR was lost. (Author abstract) (14 Refs)

47. VARIATIONS IN THE ACTIVITY OF NUCLEOLAR ORGANIZERS IN DIFFERENT TISSUES, DEMONSTRATED BY SILVER STAINING OF HUMAN NORMAL AND LEUKEMIC CELLS.

Reeves BR, Casey G, Harris H
Dept. Cytogenetics and Immunogenetics, Inst. Cancer Res., Royal Marsden Hosp., Fulham Road, London SW3 6JJ, England
Cancer Genet Cytogenet; 6(3):223-230 1982

A simple silver-staining technique that demonstrates those nucleolar organizing regions of metaphase chromosomes which are transcriptionally active during the preceding interphase (AgNORs) has been applied to cells obtained from the bone marrow and mitogen-stimulated peripheral blood lymphocyte cultures of hematologically normal individuals and patients with various forms of leukemia. In the majority of bone marrow cells from the normal controls and many of the patients, the numbers of cells with detectable AgNORs, and the staining intensities in those cells which were AG+, were markedly reduced compared with the levels found in blood lymphocytes. The numbers of cells having satellite associations and the numbers of chromosomes participating in these associations also generally reflected the proportions of AgNORs present. When patterns of bone marrow silver staining were compared between patients with leukemia, distinct differences were found which could be correlated with cytology. It is suggested that different cell types have characteristic AgNOR staining profiles, reflecting specific regulation of ribosomal RNA synthesis in particular cell lineages. AgNOR staining may indicate, therefore, the predominant cell types that divide in the bone marrows of patients with different forms of leukemia. (Author abstract) (23 Refs)

48. REARRANGEMENT IN RDNA-BEARING CHROMOSOMES IN CELL LINES FROM NEOPLASTIC CELLS.

Henderson AS, Megraw-Ripley S
Dept. Human Genetics and Development, Columbia Univ. Health Sciences, New York, NY, 10032
Cancer Genet Cytogenet; 6(1):1-16 1982

Cytological hybridization in situ and karyotypic analysis have been used to investigate positional changes in rDNA, and morphological changes in rDNA-bearing chromosomes, in a series of cell lines established from patients with various proliferative disorders. Characteristic features of chromosomes in these cell lines include extreme differences in the number of rRNA genes per locus, translocations involving rDNA, and distinct rearrangements of a large portion of the rDNA complex to a q-terminal position on acrocentric chromosomes. (Author abstract) (50 Refs)

49. ORGANIZATION, DISTRIBUTION, AND STABILITY OF ENDOGENOUS ECOTROPIC MURINE LEUKEMIA VIRUS DNA SEQUENCES IN CHROMOSOMES OF MUS MUSCULUS.

Jenkins NA, Copeland NG, Taylor BA, Lee BK
Jackson Lab., Bar Harbor, ME, 04609
J Virol; 43(1):26-36 1982

The endogenous ecotropic murine leukemia virus DNA content and integration sites were characterized for 54 inbred strains and substrains of mice by restriction enzyme digestion, Southern blotting, and hybridization with an ecotropic murine leukemia virus DNA-specific probe. More than 75% of these strains carried endogenous ecotropic proviruses which were located in at least 29 distinct integration sites in chromosomes of Mus musculus. Fourteen of these proviruses have been assigned specific locus designations. Most, but not all, of the endogenous ecotropic proviruses were structurally indistinguishable by this analysis from the prototype AKR ecotropic virus, and the distribution of these proviruses followed known [illegible]tionships among the inbred strains and substrains of mice. These results suggest that, in general, viral DNA integration preceded the establishment of inbred mouse strains and that these integrations are relatively stable. (Author abstract) (42 Refs)

50. FINE STRUCTURE OF VIRUS CHROMATIN IN THIN SECTIONS OF SV40-INFECTED CELLS: A CYTOCHEMICAL AND AUTORADIOGRAPHICAL STUDY.

Puvion-Dutilleul F, Puvion E
Institut de Rechereches Scientifiques sur le Cancer, CNRS, F-94802 Villejuif Cedex, France
J Gen Virol; 59(part2):235-244 1982

The ultrastructural organization of virus chromatin was studied within nuclei prepared from CV1 cells (cultured monkey kidney cells) lytically infected with SV40 virus (simian virus 40) by a procedure which allows a mild loosening of nucleoproteins. In addition to dispersed host components, DNA-containing nucleoplasmic structures could be identified as virus chromatin both standard staining for structure and specific staining for DNA clearly revealed in thin sections the nucleosomal structure of well-extended virus chromatin as well as alignments of virions on host chromatin. In addition, replicating and transcribing virus chromatins were abundant as revealed by high-resolution autoradiography. Therefore, the procedure of loosening of nucleoproteins used in this report also preserves the active SV40 chromatin and allows the in situ visualization in Epon sections of transcription and replication of the virus genome. (Author abstract) (25 Refs)

51. ANALYSIS OF TYPE 5 ADENOVIRUS TRANSFORMATION WITH A CLONED RAT EMBRYO CELL LINE (CREF).

Fisher PB, Babiss LE, Weinstein IB, Ginsberg HS
Dept. Microbiology, Div. Environmental Sciences, Cancer Center/Inst. Cancer Res., Columbia Univ., New York, NY, 10032
Proc Natl Acad Sci USA; 79(11):3527-3531 1982

A recently isolated cloned cell line of Fischer rat embryo fibroblasts (CREF) can be transformed at high frequency by adenovirus serotype 5 (Ad5). The CREF cells display a near diploid karyotype, do not crisscross at confluency, can be maintained at confluency for greater than 7wk at 36 C, and do not form macroscopic colonies when seeded in agar. Transformed cells are identified by their altered morphology and the presence of adenovirus DNA sequences in the transformants, which can be demonstrated by lysing cells directly on nitrocellulose filters and hybridizing with 32P-labeled Ad5 DNA (spot hybridization). The frequency of transformation at 36 C is approx 2 x 10(-4) with wild-type Ad5 and approx 2 x 10(-3) with the temperature-sensitive mutant H5ts125. Southern blot hybridization analysis indicates that five out of six wild-type Ad5-and six out of six H5ts125-transformed CREF clones isolated at 36 C Contain the complete integrated Ad5 genome. Preliminary characterization of four transformed clones (2 wild-type and 2 H5ts125) indicates that, even though transformation was done in CREF cells (a clonal cell line), they differ in their biological properties, such as saturation density and anchorage dependence. (Author abstract) (31 Refs)

52. REACTION OF ANTHRAMYCIN WITH DNA. BIOLOGICAL CONSEQUENCES OF DNA DAMAGE IN NORMAL AND XERODERMA PIGMENTOSUM CELL LINES.

Petrusek RL, Uhlenhopp EL, Duteau N, Hurley LH
(c/o Hurley) Drug Dynamics Inst., Coll. Pharmacy, Univ. Texas at Austin, Austin, TX, 78712
J Biol Chem; 257(11):6207-6216 1982

Anthramycin, an antitumor antibiotic produced by Streptomyces refuineus, produces a well defined covalent adduct with DNA and lies within the narrow groove of DNA, attached through a thermal-labile covalent animal linkage to the exocyclic amino group of guanine, without detectable distortion of the helix. This paper described results in which the biological consequences of DNA damage and repair by repair-proficient and a repair-deficient xeroderma pigmentosum (XP 12RO) cell line are presented. Anthramycin has been shown to produce excision-dependent single and double strand breaks in DNA, both of which appear to persist many hours after removal of the drug from the media. The lower ability of the xeroderma pigmentosum cell line to remove anthramycin lesions from DNA is correlated with a decreased cell survival. The biological consequences of DNA damage (genetic effects, DNA strand breakage, and cytotoxicity) are discussed with respect to the defined structure and stability of the anthramycin-deoxyguanosine adduct. (Author abstract) (31 Refs)

53. ANTIGENIC CHANGES IN NONHISTONE PROTEINS DURING AZO DYE HEPATOCARCINOGENESIS.

Schmidt WN, Gronert BJ, Page DL, Briggs RC, Hnilica LS
Dept. Biochemistry, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232
Cancer Res; 42(8):3164-3174 1982

We have investigated the appearance of specific nonhistone proteins during azo dye induced hepatocarcinogenesis in the rat. Groups of animals fed azo dye-containing diet were sacrificed at approx 3-wk intervals, portions of their livers were examined histologically, and the remaining material was fractionated into chromatin and cytoplasmic fractions. Livers of the azo dye-fed animals exhibited histological changes that have been classically attributed to the course and development of cancer; by 28 to 30 wk of treatment, nearly all animals had developed hepatomas. Heterogeneous rabbit antisera were prepared to dehistonized chromatin from several azo dye-induced hepatomas. These antisera were then used to assess various chromatins for the appearance of antigens specific for neoplasia during induced carcinogenesis using immunodetection of antigens separated electrophoretically and transferred to nitrocellulose. Changes in the immunoreactivity of liver chromosomal proteins during carcinogen treatment were evident after 3 wk, and the antigenic profiles of various chromatin samples gradually assumed the characteristics of the hepatoma. The transformation was accompanied by qualitative changes in chromosomal protein antigens, and although these antigenic species were not directly quantitated, noticeable enrichment of tumor-specific species occurred with treatment time. Immunotransfer assays of cytoplasmic fractions indicated most antigens to be specific for chromatin. Normal tissue chromatin exhibited minimal immunoreactivity, and slightly more antigenic homology was noted with regenerating liver and most transplantable tumor chromatins. Interestingly, the transplantable tumor Walker 256 carcinosarcoma was highly enriched in antigens recognized by antisera to azo dye hepatoma dehistonized chromatin. These studies establish a definite chronological correlation between the chemical induction of cancer and sequential changes in the immunological specificity of nonhistone protein antigens. (Author abstract) (56 Refs)

54. RADIATION-INDUCED THYMINE BASE DAMAGE IN REPLICATING CHROMATIN.

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Dept. Radiology, Univ. Utah Medical Center, Salt Lake City, UT, 84132
Radiat Res; 90(3):564-574 1982

When HeLa cells labeled with (3H)thymidine in their parental or mature chromatin DNA or their nascent DNA were exposed to increasing doses of gamma radiation (50-150 kilorad) a greater damage efficiency was observed in nascent chromatin DNA. Elevated thymine damage efficiency in replicating DNA was observed in both irradiated whole cells and isolated nuclei. Both the enzyme digestion (micrococcal nuclease) kinetics of DNA in mature and nascent chromatin, as well as the limit of digestion, were the same in control and irradiated cells. The size of the DNA fragments produced during enzyme digestion and the distribution of the various fragment sizes at equal digestion levels were the same in both control and irradiated cells. The rate at which the excess sensitivity of nascent chromatin DNA decreased to mature chromatin DNA levels was similar to the rate at which nascent chromatin matures, a half-time of slightly more than 2 min in both cases. Hyperthermic exposure reduced the sensitivity of nascent chromatin to parental levels. Deproteinized small fragments of nascent DNA and large fragments of mature or parental DNA were equally sensitive to thymine damage production. When nuclei were exposed to 150 kilorad of gamma radiation and then digested with micrococcal nuclease to a level which solubilizes mainly spacer DNA, the frequency of 5',6'-dihydroxydihydrothymine (tgamma)-type thymine damage in the acid insoluble DNA (principally nucleosome core DNA) was similar to that in whole, undigested chromatin DNA. These results indicate that tgamma-type thymine base damage is uniformly distributed across nucleosome core and spacer DNA. (15 Refs)

EFFECTS OF EXOGENOUS AGENTS ON CHROMOSOMES

55. ULTRASTRUCTURAL CHARACTERIZATION OF THE MEIOTIC PROPHASE. A TOOL IN THE ASSESSMENT OF RADIATION DAMAGE IN MAN.

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Mutat Res; 95(1):45-59 1982

Chromosome behavior during the major steps of the meiotic prophase is reviewed. Two processes, both initiated during leptotene, facilitate the initial matching of homologous chromosomes: the attachment of the telomeres to the nuclear envelope which reduces the freedom of telomere movement to a two-dimensional space and the concentration of the attachment sites into a restricted area of the nuclear envelope. In Homo, Triticum, Bombyx, and Coprinus, chromosome and bivalent breaks were frequent at late-zygotene, and most of the breaks were in chromosomes and bivalents that were either interlocked or clearly appeared to have been interlocked by other bivalents. In several cases, both the interlocked and the interlocking bivalents were broken at the site of the interlocking. Restriction of crossing-over to a period after the completion of pairing correction permitting the transformation of the multivalents into bivalents may account for the disomic inheritance in a number of polyploid plant species. The technique of serial sectioning and three-dimensional reconstruction is well suited for the analysis of chromosomal rearrangements too small to be characterized unambiguously by light-microscopic procedures. The analysis of the number and distribution of recombinant nodules at zygotene and pachytene in human spermatocytes, Bombyx spermatocytes, and Coprinus meiocytes has shown that the appearance of recombinant nodules coincides with the initiation of chromosome pairing and synaptonemal complex formation. Results showed that the initial random distribution of recombinant nodules during zygotene is modified in a way that tends to ensure a minimum of one nodule per bivalent at mid-late-pachytene. The homologous chromosomes in man, as well as in many other organisms, enter meiosis unpaired. (39 Refs)

56. EFFECT OF IRRADIATION DURING DIFFERENT PHASES OF THE MITOTIC CYCLE ON THE FORMATION OF SISTER CHROMATID EXCHANGES IN A CULTURE OF CHINESE HAMSTER CELLS.

Antoshchina MM, Poriadkova NA, Luchnik NV
Inst. Medical Radiology, Obninsk, USSR
Genetika; 18(4):634-638 1982

Yields of sister chromatid exchanges (SCE) and microexchanges (ME) were studied in irradiated cultures of hypodiploid Chinese hamster cells. Gamma irradiation produced a 2x increase in the yield of SCE and an 18x increase in the yield of ME. Max increases in yields of SCE and ME were observed after irradiation during the S phase of the mitotic cycle. (18 Refs) (In RUS)

57. IN VITRO EFFECT OF PULSE IONIZING RADIATION ON HUMAN BLOOD LYMPHOCYTES.

Stiazhkina TV, Khaimovich TI
No affiliation given
Med Radiol (Mosk); 27(5):68-69 1982

Cultured human peripheral blood lymphocytes were subjected to 60Co gamma irradiation (50-560 rads) or to Bremsstrahlung irradiation (30-550 rads). The yield of chromosome aberrations after pulse irradiation did not differ from that after continuous irradiation. (4 Refs) (In RUS)

58. CYTOGENETIC STUDY OF SKIN FIBROBLASTS IN A CASE OF ACCIDENTAL ACUTE IRRADIATION.

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Mutat Res; 95(1):19-30 1982

Skin fibroblasts from a heavily irradiated young Algerian who was accidentally exposed to gamma-rays from a 25 Ci iridium-192 source were studied cytogenetically. Biopsies were obtained 25 and 35 mo after irradiation. All types of classical stable chromosomal rearrangements were observed: reciprocal translocations, peri-and para-centric inversions, deletions, shifts, and 3-and 4-break translocations. The numbers of the anomalies and their distribution in the carrier cells are presented. Among the 11 paracentric inversions obtained, one, affecting the chromosome No 10, reproduced a chromosome of an ape, a part probably not occuring by chance, since only 2 paracentric inversions have occurred in the course of the formation of human chromosomes. Only one single clone had clearly developed in vivo. The clone was found in cultures initiated 25 and 35 mo after irradiation. The differences of time and place indicated that it divided and migrated in the organism. Since the frequency of highly abnormal karyotypes was only 0.13, among all abnormal karyotypes, it follows that the more abnormal karyotype, the higher is the probability of clone formation. The percentage of affected cells and the maximal number of breaks detected per cell in the various cultures are presented. Results indicated that information from cytogenetic studies of fibroblasts, even when based on stable chromosomal abnormalities, appear not sufficiently reliable for discriminating between different levels of absorbed dose. (17 Refs)

59. EFFECTS OF CONTRAST MEDIUM ON RADIATION-INDUCED CHROMOSOME ABERRATIONS.

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Radiology; 144(2):295-301 1982

The effects of contrast material (meglumine iothalamate) on radiation-induced chromosome aberrations were investigated in studies on the lymphocytes of patients who had undergone diagnostic radiography and in in vitro experiments with diagnostic x rays and 60Co gamma rays. Chromosome and chromatid aberrations were found to increase significantly with increasing concentrations of contrast material that were added at irradiation. However, the aberrations were not associated with elevation of the ratio of dicentric and ring chromosomes to the number of cells with unstable chromosome aberrations at the first mitosis. Lymphocytes irradiated in the absence of contra material did not show an increase in chromosome-type aberr tions when the agent was given in increasing concentratior during subsequent incubation, but there were greater numbei of chromatid gaps and breaks. When lymphocytes were ex posed to 400 R (103.2 mC/kg) of 60Co gamma rays, the pres ence of contrast agent did not increase the yield of dicentri and ring chromosomes, but induced a marked delay in cell pro liferation, especially in lymphocytes with more heavily dam aged chromosomes. In additional examination, the contras agent itself induced sister chromatid exchanges in lymphocytes (Author abstract) (18 Refs)

60. ENHANCED YIELD OF CHROMOSOMAL ABERRATIONS IN HUMAN PERIPHERAL LYMPHOCYTES IN VITRO USING CONTRAST MEDIA IN X-IRRADIATION.

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Mutat Res; 104(4/5):249-254 1982

Data on the mechanism for enhancement of chromosomal aberrations in human peripheral lymphocytes in vitro by contrast media in x-irradiation are presented. The absorbed radiation dose in blood containing contrast medium was calculated on the basis of dose-enhancement factors. Blood from healthy donors was treated with contrast medium only, x-rays only, or x-rays with contrast medium added to blood prior to irradiation. Contrast medium combined with x-rays increased radiation-induced chromosomal aberration yield, depending on the iodine concentration; the effect was the result of enhancement of radiation dose due to the photoelectric effect of iodine. (8 Refs)

61. KINETICS OF INDUCTION OF SISTER-CHROMATID EXCHANGES BY X-RAYS THROUGH TWO CELL CYCLES.

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Mutat Res; 94(2):359-368 1982

Sister chromatid exchange (SCE) induction by x-rays delivered at various times during the two cell cycles needed to obtain harlequin-stained chromosomes (metaphases II) was studied in V79 Chines hamster cells that were allowed to incorporate 5-bromo-2'-deoxyuridine (BrdUrd) for only 6 hr during the first cell cycle. A linear dose-response was obtained when the x-irradiation was performed just prior to the BrdUrd addition. When the x-irradiation was performed during the first cell cycle, the number of SCE progressively increased, and then reached a plateau during the BrdUrd incorporation. The kinetics of SCE induction with N-methyl-N'-nitro-N-nitrosoguanidine was different: no increase was observed during the first cell cycle, and the SCE frequency significantly decreased with the completion of the S phase of both the first and the second cell cycles. After the addition of BrdUrd, the G1 phase appeared first and the G2 phase appeared at the end. The cell cycle was longer for the x-irradiated cells than that for the unirradiated controls, and at the ordinate of 50% tritium-labeled metaphases II, the S-phase duration was 7.5 hr for the former and 6.5 hr for the latter. While the number of dicentric chromosomes decreased when cells passed from G1 to S, the frequency of chromosomal aberrations remained stable until the late S phase and a small decrease was observed in G2. The chromatid-type aberration frequency was enhanced by a factor of 3 between G1 and early-middle S. Approx 25% of the cells showed no aberration when x-irradiation was performed prior to the S phase. (16 Refs)

62. ULTRAVIOLET-INDUCED CHROMATID EXCHANGES IN V-79 CELLS WITH NORMAL AND BRDURD-SUBSTITUTED DNA AND THE INFLUENCE OF INTERCALATING SUBSTANCES AND CYSTEINE.

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Radiat Res; 90(3):538-546 1982

The effect of UV irradiation on the sister chromatid exchange (SCE) frequency of bromodeoxyuridine (BrdUrd)-substituted DNA of V-79 cells was investigated. Cysteine (10(-3) M) did not influence UV-induced SCE frequency of unsubstituted DNA. Cysteine did cause a slight but statistically significant reduction of UV-induced SCEs in BrdUrd-substituted DNA. Since postirradiation treatment with cysteine also led to a reduction in SCE frequency, reactions other than sulfhydryl radical scavenging appeared to be at work. Proflavine (5 x 10(-6) M) did not produce a change in SCE frequency in controls or irradiated cells with unsubstituted DNA. At 10(-5) M, proflavine increased SCE frequency in these cells and in cells containing substituted DNA. These results indicate that the induction of chromosome aberrations or SCEs by UV light in BrdUrd-substituted DNA occur independently and that UV-induced single-strand breaks are more involved in the induction of chromosome aberrations and contribute to the formation of SCEs. (26 Refs)

63. CYSTEAMINE PROTECTION OF SCES INDUCED BY UV AND FLUORESCENT LIGHT.

Bianchi M, Bianchi N, Cortes L, Reigosa M
Instituto Multidisciplinario de Biologia Celular (IMBICE), C.C. 403, 1900 La Plata, Argentina
Mutat Res; 104(4/5):281-286 1982

Effects of cysteamine (Cys) on frequency of sister chromatid exchanges (SCE) in 5-bromo-2'-deoxyuridine (BUDR)-substituted cells exposed to UV or fluorescent light were studied in CHO cells. Data on av SCE/chromosome and the number of chromosomes analyzed in each treatment are presented. Results indicated that Cys does not produce any significant increase in SCE over the basal frequencies obtained with BUDR. However, UV and fluorescent light induced a 3-4-fold increase in the frequency of exchanges. Treatment with Cys during UV and fluorescent light irradiation produced a drastic reduction in SCE. (28 Refs)

64. INVESTIGATIONS ON THE MUTAGENIC AND CLASTOGENIC ACTIVITY OF RESORCIN. CYTOGENETIC FINDINGS FROM DIFFERENT TYPES OF HUMAN CELLS.

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Arzneim Forsch; 32(5):533-536 1982

The suspected clastogenic effect of m-dihydroxybenzene (resorcin), a phenol derivate, was investigated by analyzing three different types of human cells: (1) lymphocyte cultures from blood of healthy blood donors with normal karyotype (46, XY); (2) lymphocyte cultures from patients with a proven chromosome abnormality (trisomy 21, karyotype: 47, +21); and (3) cultures of amniotic cells with normal karyotype (46,XX and 46,XY). In all three cell systems resorcin induces secondary chromosome aberrations. The number of cells with aberrations increases with the concentration of the substance and duration of action. The three cell systems tested showed a different sensibility to resorcin. Lymphocytes with trisomy 21 were more sensitive than the same cell type with a normal karyotype. Both types of lymphocytes were less sensitive to resorcin than amniotic cells. The types of structural chromosome aberrations observed in these investigations as well as the concentration of the test substance, which had to be added to induce a clastogenic effect, demonstrated that resorcin has to be regarded as a weak mutagenic substance. (Author abstract) (16 Refs) (In GER)

65. CHROMOSOMAL ABERRATIONS INDUCED BY ETHYLENE OXIDE IN A HUMAN AMNIOTIC CELL LINE IN VITRO.

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Mutat Res; 104(4/5):255-260 1982

Effects of ethylene oxide (EO) on the induction of chromosomal aberrations were studied in the human FL cell line and the results are discussed. The range of EO doses, 5, 7, and 10 milliM (mM)/hr, which led to cell survival of 58, 25, and 9.2% were used. Cells kept in phosphate-buffered saline for the same length of time served as controls. The majority of induced aberrations were of the chromatid type such as: gaps, breaks, exchanges, and 'complexes'. Several metaphases with aberrations were observed in the control cultures at each fixation time. Significant increase as a function of EO doses was observed in the frequencies of chromosomal aberrations of all categories. The number of aberrant metaphases in the cultures treated at 5, 7, and 10 mM/hr was 21.3, 65.6, and 74.9%, respectively, at 48-hr fixation time. The number of aberrations/metaphase increased in treated cultures, 2x for 5 mM/hr, 10x for 7.5 mM/hr, and 36x for 10 mM/hr EO. The number of observed breaks increased 4-, 10-, and 50-fold with increasing concentration of EO. The number of chromatid exchanges increased for approx 2-, 10-, and 20-fold in EO-treated cultures. Multiple aberrations scored as 'complexes' appeared only in 7.5 mM/hr-treated cells and their number increased 10-fold in 10 mM/hr-treated cells. The frequencies of induced aberrations varied with the post-treatment time. Except for the gaps, the observed frequencies of chromosomal aberrations decreased slowly and gradually until 96 hr after treatment. A dose of 12.5 mM/hr appeared to be toxic (4% survival level) for the production of good metaphase chromosome preparations. (24 Refs)

66. METABOLIC ACTIVATION OF BENZO[A]PYRENE, AFLATOXIN B1, AND DIMETHYLNITROSAMINE BY A HUMAN HEPATOMA CELL LINE.

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Mutat Res; 94(2):339-348 1982

The frequency of sister-chromatid exchanges (SCE) was measured in normal human fibroblasts (TIG-II) co-cultivated with human hepatoma huH-1 cells to assess the genotoxic effect of activated chemicals aflatoxin B1 (AFB), benzo[a]pyrene (B[a]P), N,N-dimethylnitrosamine (DMN), and 1,2-benzanthracene. When huH-1 cells were treated with 13 uM BA for 24 hr, aryl hydrocarbon hydroxylase activity was induced to 920 picomoles/mg protein/hr, which was approx 24x higher than the basal level. SCE frequency in TIG-II cells changed depending on the inoculum ratio of huH-1 cell to TIG-II cells in the co-culture containing 5 uM AFB. When the inoculum size of huH-1 cells was half that of TIG-II cells, the SCE frequency in TIG-II cells was markedly enhanced over the control level that remained in plateau even in the cultures with larger inocula of huH-1 cells. In the co-culture, the SCE frequency was increased depending on the dose of B(a)P: 0.1 and 12.5 uM of B(a)P induced 7.2 and 10.7 SCE/metaphase, respectively. In the cultures of TIG-II cells only, 0.5 uM of B(a)P showed no significant increase of SCE, while 2.5 and 12.5 uM of B(a)P slightly elevated the SCE frequency over the control level. Treatment with DMN increased the incidence of SCE far more efficiently in the co-cultivation than in cultures of TIG-II cells only. The SCE frequency induced by 0.4 milliM (mM) of DMN in the cultures with huH-1 cells was comparable with that induced by 10 mM of DMN without huH-1 cells. (41 Refs)

67. BASELINE AND MITOMYCIN-C-INDUCED SISTER CHROMATID EXCHANGES IN A MELANOMA AND A COLON TUMOR CELL LINE.

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Cancer Genet Cytogenet; 6(3):243-248 1982

Baseline and mitomycin C (MMC)-induced sister chromatid exchanges (SCEs) in two human tumor cell lines (a colon tumor and a melanoma) and in a normal fibroblast cell line were analyzed and compared. The tumor cells showed numerical and structural chromosomal abnormalities. Their baseline SCE rate was slightly, but not significantly, higher than that of the control. Each tumor cell line showed a dose-dependent increase in SCE frequency above the spontaneous level in its own specific manner. The response in the melanoma cell was consistently below that of the control, but only the response to the highest dose of MMC (10(-9) M) was significantly lower than that of the control. The response of the colon tumor cells varied with respect to that of the control. Thus, it appears that karyotypic instability in tumor cells is not necessarily associated with elevated baseline or induced SCE/chromosome rates. In addition, within each cell line dose group, the SCE frequency was proportional to the number of chromosomes. Thus, the SCE/chromosome is a better expression of genetic damage than SCE/metaphase in analyses involving heteroploid cells. (Author abstract) (14 Refs)

68. CHROMOSOME ABERRATIONS AND SISTER CHROMATID EXCHANGES IN CULTURED HUMAN LYMPHOCYTES TREATED WITH DIETHYLSTILBESTROL DIPROPIONATE.

Dzhangulashvili NA
Medical Inst., Tbilisi, USSR
Tsitol Genet; 16(2):24-29 1982

Mutagenic activity of diethylstilbestrol dipropionate (DES) at different concentrations was studied in cultured human peripheral blood lymphocytes. DES at 1.3 x 10(-6) M and 1.3 x 10(-5) M increased the incidences of aberrant metaphases (1.94% and 4.80%, respectively, compared with 0.49% after exposure of the cells to DES at 1.3 x 10(-7) M and 0.23% in untreated control cells). The incidences of sister chromatid exchanges after exposure of the cells to DES at 1.3 x 10(-6) M and 1.3 x 10(-5) M were 12.37% and 11.78%, respectively, compared with 7.17% after exposure of the cells to DES at 1.3 x 10(-7) M and 7.98% in untreated control cells. (33 Refs) (I RUS)

69. COMPARATIVE EFFICACY OF INDUCTION OF SISTER CHROMATID EXCHANGES BY ETHYLENE IMINE DERIVATIVES IN CULTURED HUMAN LYMPHOCYTES.

Listopad GG, Chebotarev AN
Inst. Medical Genetics, Moscow, USSR
Tsitol Genet; 16(2):34-38 1982

Mutagenic activities of six N-phosphoryl derivatives of ethylene imine (EI) were studied in cultures of human peripheral blood lymphocytes. The EI derivatives produced dose-dependent increases in incidences of sister chromatid exchange (SCE). Mutagenic activities of the polyfunctional EI derivatives were significantly greater than those of the monofunctional derivatives. The linear increase that was observed in the yield of SCE after exposure of the cultures to monofunctional derivatives indicated that the formation of cross-links was not a necessary requirement for SCE induction. (5 Refs) (In RUS)

70. CHROMOSOMAL ABERRATIONS AND SISTER-CHROMATID EXCHANGES (SCES) IN PATIENTS UNDERGOING LONG-TERM IMURAN THERAPY.

Kucerova M, Kocandrle V, Matousek V, Povlikova Z, Reneltova I
Pediatric Clinic, Postgraduate Medical Inst., Videnska 800, 14629 Prague 4, Krc, Czechoslovakia
Mutat Res; 94(2):501-509 1982

Seventeen patients under extended imuran therapy (50 mg/day) were cytogenetically analyzed for the induction of structural chromosomal aberrations and sister-chromatid exchanges (SCE). Thirteen patients also received prednisone 20 mg/day. Most of the patients had an increase in the frequency of both structural aberrations and SCE. However, the results were not homogeneous, and no clear-cut relationship was found between the length of therapy and the number of aberrations. In some patients it was not possible to find any relation between the level of structural aberrations and SCE. (20 Refs)

71. ANTI-TUMOR ALKYLATING AGENTS ACT SYNERGISTICALLY WITH METHYLXANTHINES ON INDUCTION OF SISTER-CHROMATID EXCHANGE IN HUMAN LYMPHOCYTES.

Mourelatos D, Dozi-Vassiliades, Granitsas A
Dept. General Biology, Faculty Medicine, Aristotelian Univ., Thessaloniki, Greece
Mutat Res; 104(4/5):243-247 1982

Combination of chlorambucil (CBC), melphalan (MEPH), cis-platinum(II) diamine dichloride (cis-PtII), and caffeine, and theophylline and diphylline alone and in combination with CBC, MEPH, and cis-PtII were used upon normal human lymphocytes to determine sister-chromatid exchange (SCE). Results showed that when methylxanthine was added to the cultures exposed to an alkylating agent at doses sufficiently high to induce SCE, the effect of methylxanthine was synergistic, the SCE level being much higher than that expected by the simple addition of the effects of the agent and methylxanthine. Any methylxanthine alone at concentrations used throughout the experiments (100 ug/ml) induced only a small increase in SCE rates. The relative ability to potentiate the production of SCE induced by cis-PtII (100 nanog/ml) appeared to be: caffeine greater than theophylline greater than diphylline. The difference between the results on human lymphocytes and the findings on rodent material might be accounted for by the different cell types used. In cultured rodent cells, in which only a poor pre-replication repair system exists, caffeine interferes with post-replication repair, which may be responsible for the decrease observed in SCE frequency. (15 Refs)

72. EFFECT OF TEMPERATURE VARIATION ON SISTER-CHROMATID EXCHANGE AND CELL-CYCLE DURATION IN CULTURED HUMAN LYMPHOCYTES.

Abdel-Fadil MR, Palmer CG, Heerema N
Dept. Physiology, Faculty Medicine, Assiut Univ., Assiut, Egypt
Mutat Res; 104(4/5):267-273 1982

The relationship of temperature variation and cell-cycle duration and their influence on sister chromatid exchange (SCE) frequency in human lymphocyte cultures was studied in peripheral blood from 12 healthy subjects. Both SCE frequency and cell-cycle distribution were affected by a decrease in temperature, but only the SCE levels were affected by an increase in temperature from 37 to 39 C. The incidence of SCE was significantly increased when the incubation temperature was lowered to 35 C (mean 13.39 +-2.03/cell) compared to control cells (mean 9.49 +-1.77/cell). (33 Refs)

73. SISTER CHROMATID EXCHANGES INDUCED BY METHYLXANTHINES CONTAINED IN COFFEE, TEA AND COCOA.

Renner HW
Federal Res. Centre for Nutrition, Engesserstr. 20, D-7500 Karlsruhe, W. Germany
Experientia; 38(5):600 1982

Methylxanthines consumed daily by most humans were investigated for induction of sister chromatid exchanges (SCE). Effects observed in this highly sensitive in vivo system decreased in the order theophylline/theobromine greater than caffeine greater than paraxanthine greater than monomethylxanthines. (Author abstract) (19 Refs)

74. 5-BROMODEOXYURIDINE INDUCED SISTER CHROMATID EXCHANGE FREQUENCIES IN PRIMATE LYMPHOCYTES.

Barnett RI, Wallace JA
Dept. Anatomy, Queen's Univ., Kingston, Ontario K7L 3N6, Canada
Experientia; 38(5):542-543 1982

Comparisons of SCE frequencies at various BrdUrd concentrations showed significant interspecies differences with human lymphocytes being the most sensitive. (Author abstract) (16 Refs)

75. RESTITUTION OF CHROMATID AND ISOCHROMATID BREAKS INDUCED IN THE G2 PHASE BY ACTINOMYCIN D.

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Dept. Cell Biology, Univ. Texas M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Environ Mutagen; 4(3):259-265 1982

Lymphocytes treated with actinomycin D (AD; 3.5 ug/ml) for 90 min showed single chromatid breaks, a high frequency of chromatid exchange figures (translocations, inversions, rings) and closed isochromatid breaks. These changes indicated that a type of DNA repair leading to chromosome aberrations had occurred prior to cell fixation. At least some of the breaks that occur after AD treatment in G2 represent true DNA damage and were not merely artifacts of fixation. (8 Refs)

76. THE EFFECTS OF POST-TREATMENTS WITH CAFFEINE DURING S AND G2 ON THE FREQUENCIES OF CHROMOSOMAL ABERRATIONS INDUCED BY THIOTEPA IN ROOT TIPS OF VICIA FABA AND IN HUMAN LYMPHOCYTES IN VITRO.

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Mutat Res; 104(4/5):323-330 1982

Effects of caffeine post-treatments during S phase and G2 on the frequencies of chromosomal aberrations induced by thiotepa (TP) were studied in root tips of Vicia faba and in cultures of human lymphocytes in vitro. One type of post-treatment consisted of a 21-hr treatment with 7.5 x 10(-4) M caffeine, (begun at 23 hr after the TP treatment and terminated at 6 hr prior to harvesting the cultures), whereas the other consisted of a 3-hr treatment with 2.5 x 10(-3) M caffeine given immediately prior to harvesting. In V faba, the 'S pulse' was highly effective in enhancing TP-induced chromosome damage (the total aberration frequency being greater than 5x higher in the presence than in the absence of caffeine), whereas the 'G2 pulse' gave no enhancement. In human lymphocytes, a considerable potentiation was obtained when the caffeine post-treatment was given during the last 3 hr prior to culture harvesting. An increase in the total frequency of TP-induced chromosomal aberrations was also obtained when the lymphocytes were post-treated during the S phase, but this increase was small (1.7x the effect in the TP control) in comparison with that produced by the G2 treatment in the same material (2.5x the TP control) or with that produced by the 'S pulse' in V faba (5.3x the TP control). In V faba, chromatid exchanges were strongly enhanced and chromatid breaks only little affected, whereas in human lymphocytes the opposite was observed. Results indicated that the great majority of the TP-induced chromatid breaks are formed during G2 in human lymphocytes. (14 Refs)

77. CELLULAR REPLICATION KINETICS AND PERSISTENCE OF SISTER CHROMATID EXCHANGE-INDUCING LESIONS IN NORMAL AND LYMPHOMA AKR CELLS FOLLOWING EXPOSURE TO 1,3-BIS(2-CHLOROETHYL)-1-NITROSOUREA.

Biegel JA, Conner MK, Boggs SS
Univ. Pittsburgh Sch. Medicine, RC510 Scaife Hall, Pittsburgh, PA, 15261
Cancer Res; 42(7):2816-2820 1982

The present studies were designed to evaluate the role of cell cycle time and time of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) administration on the persistence of sister chromatid exchange (SCE)-inducing lesions in normal and lymphoma second- and third-division AKR bone marrow cells. Normal second-division cells harvested from mice given injections of BCNU at the start of an 18-, 24-, or 28-hr 5-bromo-2-deoxyuridine (BrdUrd) infusion exhibited similar linear dose-dependent increases in SCE frequencies. The faster-cycling lymphoma cells, harvested after 18-hr BrdUrd infusion, had significantly higher base-line and BCNU-induced increases in SCE frequencies than did normal cells. Dose-dependent increases in SCE frequencies were demonstrated in third-division normal and lymphoma cells from mice infused with BrdUrd for 24 or 28 hr. BCNU dose-dependent increases in SCE frequencies were also observed following injection of BCNU 8 hr after the start of BrdUrd infusion. The unexpectedly higher levels of SCEs for both normal and lymphoma cells by this treatment protocol may be due to SCEs occurring at the same site in successive divisions in BrdUrd. Lower nonreciprocal SCE frequencies were observed in third-division cells relative to SCE frequencies in second-division cells; a possible consequence of the cytotoxicity of BCNU. Injection of BCNU produced significant changes in the proportions of normal and lymphoma cells completing one, two, or three or more divisions in BrdUrd. Lymphoma cells were consistently more sensitive to the specific type(s) of BCNU-induced damage leading to SCEs and cell death than were normal cells. These studies indicated that differences in SCE response were not due to cell cycle time, time of drug administration, or potential for repair. It is therefore suggested that increased sensitivity of lymphoma vs normal cells may be due to increased cellular uptake of BCNU. (11 Refs)

78. SISTER CHROMATID EXCHANGE INDUCTION IN TWO CELL LINES.

Mitchell GA, Meher-Homji KM, Baker RS

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Environ Mutagen; 4(3):267-270 1982

In the absence of the S9 metabolizing system, benzo(a)pyrene induced sister chromatid exchanges (SCE) in Chinese hamster lung (Don) cells but not in Chinese hamster ovary cells (CHO). Addition of S9 to CHO cells is necessary to obtain levels of SCE/metaphase similar to those induced in Don cells. It is suggested that Don cells still have an intact intracellular enzyme system capable of metabolizing biologically inert compounds into an active form. (12 Refs)

79. EFFECT OF DIESEL EXHAUST EMISSIONS, PARTICULATES, AND EXTRACT ON SISTER CHROMATID EXCHANGE IN TRANSPLACENTALLY EXPOSED FETAL HAMSTER LIVER.

Pereira MA, McMillan L, Kaur P, Gulati DK, Sabharwal PS

Health Effects Res. Lab., United States Environmental Protection Agency, 26 W. St. Clair St., Cincinnati, OH, 45268

Environ Mutagen; 4(3):215-220 1982

The genotoxic activity of diesel exhaust emissions was evaluated by means of the sister chromatid exchange (SCE) assay and the mitotic index (MI) in fetal liver cells from Syrian hamster exposed in utero. SCE was determined in pregnant hamsters in which a pellet of bromodeoxyuridine was implanted under the skin in the interscapular area on day 13 of gestation. Two hr later the test substance was administered ip; 18 hr after treatment, the animals were killed. Exposure to diesel exhaust emissions from day 5-13 of gestation did not alter SCE or MI. The positive control, 100 mg/kg benzo(a)pyrene caused a doubling of SCE and a reduction of MI. A methylene chloride extract of the diesel particulate matter caused a dose-dependent increase in frequency of SCE with a doubling in incidence caused by approx 320 mg/kg, equivalent to one-quarter of the LD50. The extract and particulate matter caused a dose-dependent decrease in the MI of fetal liver. The in utero SCE analysis was demonstrated to be a sensitive assay for the detection of the genotoxic agents present in a complex mixture, of an extract of diesel particulate matter. (21 Refs)

80. ALKYLARYLNITROSOUREAS: STABILITY IN AQUEOUS SOLUTION, PARTITION COEFFICIENT, ALKYLATING ACTIVITY AND ITS RELATIONSHIP TO SCE INDUCTION IN CHINESE HAMSTER V79-E CELLS.

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Arch Geschwulstforsch; 52(5):371-377 1982

The alkylating activity, chemical stability, and partition coefficient were determined for eight nitrosourea derivatives. Test compounds were compared with 1-methyl-1-nitrosourea and 1-ethyl-1-nitrosourea. Decomposition in aqueous soln was influenced by the 1-N and 3-N substituents. The alkylating activity of mono- and di-substituted nitrosoureas correlated roughly with induction of sister chromatid exchanges (SCE) in Chinese hamster V79-E cells. However, 1-methyl-3-naphthyl-1-nitrosocarbamate had low alkylating activity but high SCE-inducing activity. 1,3-Dimethyl-3-phenyl-1-nitrosourea had no detectable alkylating activity but was the strongest SCE inducer. (28 Refs)

81. SISTER CHROMATID EXCHANGE INDUCED BY SHORT-LIVED MONOADDUCTS PRODUCED BY THE BIFUNCTIONAL AGENTS MITOMYCIN C AND 8-METHOXYPSORALEN.

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Environ Mutagen; 4(3):239-247 1982

To determine if DNA crosslinks are involved in the induction of sister chromatid exchange (SCE), Chinese hamster ovary cells were exposed to two bifunctional alkylating agents mitomycin C (MMC) and 8-methoxypsoralen (MOP), and their monofunctional derivatives decarbamoyl mitomycin C (dcMMC) and angelicin (ANG). With all the agents used, the av number of SCE/cell increased with increasing concentration. Both MMC and dcMMC had a similar effect in inducing SCE. MOP + UVA was more active in producing SCE than ANG + UVA. MMC and dcMMC were also very similar in the lifetime of lesions leading to SCE formation. MOP + UVA was remarkably similar to MMC and dcMMC in the lifetime of lesions leading to SCE formation. ANG + UVA, however, behaved in a different manner in that it caused longer-lived lesions in cells with comparable numbers of SCE. Thus, at the lowest concentration of ANG tested, the number of SCE produced during the second, as well as the first, cell cycle was increased. The elevated frequency of single SCE did not change as the concentration of ANG was increased. This behavior, like that of methanesulfonate, indicates that several different types of DNA lesions are capable of SCE induction. (35 Refs)

82. ELIMINATION OF METABOLIC CO-OPERATION AND THE INDUCTION OF SISTER CHROMATID EXCHANGES ARE NOT PROPERTIES COMMON TO ALL PROMOTING OR CO-CARCINOGENIC AGENTS.

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Carcinogenesis; 3(5):499-503 1982

High densities of wild-type, 6-thioguanine sensitive V79 cells reduce the recovery of 6-thioguanine resistant (6TGR) cells when they are co-cultivated. This metabolic cooperation effect has been reported previously to be eliminated by the tumor promoter 12-O-tetradecanoylphorbol-13-acetate and the accompanying enhancement of 6TGR colony recovery has been postulated as a rapid assay for tumor promoters. Elimination of metabolic cooperation, however, does not appear to be a characteristic of either the promoting agents anthralin, iodoacetic acid, oleic acid and delta-hemolysin or the co-carcinogenic/carcinogenic agents griseofulvin, diethylstilbestrol and stilbestrol diproprionate. Moreover, with exception of stilbestrol diproprionate, none of these agents induce sister chromatid exchanges, but are all, with the exception of delta-hemolysin, associated with limited numerical chromosome changes and in four cases low level aberration induction. None of the agents were mutagenic. (Author abstract) (53 Refs)

83. ENHANCEMENT OF SISTER-CHROMATID EXCHANGES BY TUMOUR PROMOTERS.

Ray-Chaudhuri R, Currens M, Iype PT
NCI-Frederick Cancer Res. Facility, Frederick, MD, 21701
Br J Cancer; 45(5):769-777 1982

The effect of the tumor promoters TPA, phenobarbitone and saccharin on the production of sister-chromatid exchanges (SCE) was studied. TPA produced a small but significant increase of SCE in Chinese hamster cell lines V-79 and CHO, and in a hybrid clone formed by fusion of CHO with rat liver epithelial cells. The enhancement of SCE by TPA was not affected by the type of culture medium, heat-inactivated bovine serum, or the batch of TPA. In the presence of exogenous L-cysteine the enhancement of SCE was reduced. TPA also increased the uptake of 2-deoxyglucose by the cells, to an extent similar to that of the SCE enhancement. This enhancement of SCE by TPA may be explained partly through the formation of free radicals, and partly through alterations in the cell-surface membrane and/or a transient delay in the cell-cycle progression. The other tumor promoters, phenobarbitone and saccharin, also enhanced both SCE and the uptake of 2-deoxyglucose in V-79 cells. (Author abstract) (48 Refs)

84. TUMOR PROMOTER 12-O-TETRADECANOYL-PHORBOL-13-ACETATE ENHANCES SISTER CHROMATID EXCHANGES AND NUMERICAL AND STRUCTURAL CHROMOSOME ABERRATIONS IN PRIMARY MOUSE EPIDERMAL CELL CULTURES.

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Cancer Lett; 16(1):7-17 1982

The induction of a moderate increase in sister chromatid exchanges (SCEs) and pronounced numerical and structural chromosome aberrations in newborn mouse epidermal cells in primary culture 12-O-tetradecanoyl-phorbol-13-acetate (TPA) is reported. While only 1.2-1.4x increases in SCEs were observed in epidermal cultures, 2-3x increases in the number of metacentric chromosomes, chromatid and isochromatid breaks and fragments were seen after TPA treatment. TPA consistently altered chromosome numbers and caused pronounced structural aberrations. TPA markedly enhanced the number of aneuploid cells. The percentage of detectable chromatid and chromosome breaks and chromosome rearrangements such as tri- and quadriradials, ring and dicentric chromosomes was markedly enhanced after TPA. Chromosomes more frequently involved in breaks were numbers 1, 2, 4, 5, 8 9, and 10 whereas in exchange figures medium sized chromosomes such as 9, 10 and 13 were preferentially involved. Centromeric splitting was also observed after TPA. These chromosomal alterations were not seen with 4-O-methyl-TPA. (37 Refs)

85. SISTER CHROMATID EXCHANGE RESPONSE OF HUMAN DIPLOID FIBROBLASTS AND CHINESE HAMSTER OVARY CELLS TO DIMETHYLNITROSAMINE AND BENZO(A)PYRENE.

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Dept. Pediatrics, McMaster Univ. Health Sciences Centre, Hamilton, Ontaria L8N 3Z5, Canada
Environ Mutagen; 4(3):203-214 1982

A study was undertaken to examine the possibility that Chinese hamster ovary (CHO) and human diploid fibroblasts may not show the same sensitivity to well known carcinogens benzo(a)pyrene (BP) and dimethylnitrosamine (DMN), using a metabolic activation system and sister chromatid exchange (SCE) analysis. Metabolic activation in the tests was accomplished with a microsomal fraction from rats induced with Aroclor 1254. The human diploid lines employed were IMR-90, WI-38, and S-3299. For both BP and DMN the human cells and CHO cells showed dose-response slopes that were significantly different from zero, except for CHO cells treated with BP for 1 hr and S-3299 cells treated with DMN. While the responses of the human and CHO cells to BP, and the responses of the human cells to BP and DMN were similar, the dose-response of the human cells to DMN was statistically less significant than that of CHO cells. Reducing the period of treatment of CHO cells from 1.0 hr to 0.5 hr had no effect on the slope of the dose-response curves for BP and DMN. The observed differences between human and CHO cells may reflect differences in the fate of metabolic intermediates of DMN. (38 Refs)

86. CHROMOSOMAL REARRANGEMENT AND CARCINOGENESIS.

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Mutat Res; 98(3):249-264 1982

Chromosomal rearrangement (CR) associated with carcinogenesis, CR in human cancer-prone syndromes, carcinogenic CR, induction of CR, role of CR in carcinogenesis, and mechanism of carcinogenesis were examined. To determine whether the ability to induce CR is a general property of carcinogens, 61 carcinogens (45 Ames test-positive, 16 Ames test-negative) were examined. Obtained data supported the hypothesis that the ability to induce CR is correlated with carcinogenesis. The association of CR with human and rodent cancers and with human cancer-prone systems further support the hypothesis. Also suggestive was the finding that DNA from non-malignant cells can transform other non-malignant cells, under conditions that may involve CR. Evidence suggesting that some DNA lesions can act as preferential sites for the initiation of DNA exchange is discussed. In addition, the results of several experiments suggested that carcinogens, at least radiation, can act epigenetically to induce recombinant activity. Apparently, carcinogens can act to induce CR by creating or revealing sites of DNA for recombination or by inducing or activating cellular systems resulting in a stimulation of recombination. The ploidy-change class of CR can allow either the amplification of genes, by increasing ploidy, or the expression of recessive genes, by decreasing ploidy. Thus all classes of CR may affect gene expression, and therefore, carcinogenesis. Proposal concerning some of the steps in carcinogenesis, implying that malignancy may be a result of the expression of cellular 'cancer genes' which are either not expressed or insufficiently expressed in normal cells because they are linked with a poorly transcribing control region, is presented. (57 Refs)

87. INTERCALATING SUBSTANCES DO NOT INDUCE SISTER-CHROMATID EXCHANGES (SCES) IN VIVO.

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Abteilung Klinische Genetik, Oberer Eselsberg, D-7900 Ulm, W. Germany
Mutat Res; 104(4/5):261-266 1982

Acridine derivative, proflavine (PF), and phenothiazine derivatives, methylene blue (MB) and chlorpromazine (CPZ) were investigated in vivo (Chinese hamsters, 6-12 mo old) in the sister-chromatid exchange (SCE) test for the demonstration of a possible DNA-damaging effect. To evaluate the cellular proliferation, the distribution of metaphases of the first, second, and third generations were determined in 200 mitoses each. Cells that had replicated their DNA exclusively before the implantation of 5-bromodeoxyuridine could not be distinguished from the first metaphases, and cells that had gone through more than three cell cycles were counted as third mitoses. PF as well as MB and CPZ did no lead to a significant induction of SCE in the bone marrow of Chinese hamster. CPZ was tested up to a concentration corresponding to 4x the therapeutic dose in man. PF and MB were tested in vivo up to the same concentration level without showing any effect. An increase of the dose was limited by the solubility of the substances. The distribution of the first, second, and third mitoses showed that the proliferation of the cells analyzed in the bone marrow was not delayed in comparison with the control. To exclude artifacts from the experimental procedure, cyclophosphamide (CP) was tested as a positive control. CP led to a pronounced increase in the SCE frequencies without impeding the proliferation of the cells. (13 Refs)

88. MUTAGENICITY TESTS AND IN VITRO TRANSFORMATION ASSAYS ON TRIETHANOLAMINE.

Inoue K, Sunakawa T, Okamoto K, Tanaka Y
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Mutat Res; 101(4):305-313 1982

The mutagenicity and cell-transforming activities of triethanolamine were examined by measuring induction of DNA damage in Bacillus subtilis, mutagenicity in Salmonella typhimurium and Escherichia coli, production of chromosomal aberrations in Chinese hamster cells, and transformation of hamster embryo cells. Diethanolamine and monoethanolamine were also examined for induction of transformation. The results suggest that triethanolamine may not produce genotoxic effects by reaction with DNA and consequent induction of changes in DNA structure and function. The increased incidence of tumors induced in female mice by triethanolamine may be a secondary or indirect result of some specific cytotoxic effect. (20 Refs)

89. MUTAGENICITY STUDY OF FRIED SAUSAGES IN SALMONELLA, DROSOPHILA AND MAMMALIAN CELLS IN VITRO AND IN VIVO.

Gocke E, Eckhardt K, King MT, Wild D
Inst. Molecular Biology, Univ. Aarhus, 8000 Aarhus, Denmark
Mutat Res; 101(4):293-304 1982

An extract of pan-fried sausage was tested in an array of systems, including the Salmonella/microsome test, the Drosophila sex-linked recessive lethal test, tests for induction of sister-chromatid exchange and point mutations in V79 Chinese hamster cells, the micronucleus test, the intrasanguine host-mediated assay, and the mammalian spot test. Results suggest that mice and possibly mammals in general are less sensitive than Salmonella towards the mutagens produced during frying of meat. The mutagenic risk of traces of promutagens in fried meat is orders of magnitude lower than would be estimated using the Ames plate test as a guideline. However, genetic activity of the mutagenic principles of fried meat in mammalian systems cannot be excluded. (29 Refs)

90. A STUDY ON THE MUTAGENICITY OF PHENOBARBITONE USING THE MICRONUCLEUS TEST IN SWISS MICE.

Nandan SD, Rao S
Dept. Genetics, Osmania Univ., Hyderabad 500 007, India
IRCS Med Sci [Cancer]; 9(10):937-938 1981

The chromosome-breaking potential of phenobarbitone in bone marrow cells of Swiss mice was assessed employing the micronucleus test. A statistically significant and dose-dependent increase in the frequency of micronuclei was observed in the polychromatic and normochromatic erythrocytes at drug doses of 84 and 126 mg/kg body wt, while no significant increase in the micronulcei was detected with 42 mg/kg. Results indicated that phenobarbitone is capable of causing chromosome damage in the bone marrow cells of mice. (14 Refs)

91. DEVELOPMENT OF NECROSES, VIRUS ACTIVATION AND GIANT CELL FORMATION AFTER TREATMENT OF EHRLICH ASCITES TUMOR WITH METALLOCENE DICHLORIDES.

Kopf-Maier P
Institut Anatomie, Freien Universitat Berlin, Konigin-Luise-Strasse 15, D-1000 Berlin 33, W. Germany
J Cancer Res Clin Oncol; 103(2):145-164 1982

Light-microscopic and ultrastructural alteration patterns are investigated after in vivo treatment of EAT with the cytostatic agents vanadocene dichloride (VDC) and titanocene dichloride (TDC). Both substances induce mitotic aberrations, eg, pyknotic metaphases, lagging chromosomes during anaphase, and multipolar mitotic figures. The appearance of mononucleate and, occasionally, multinucleate giant cells is observed mainly 48-96 hr at. The first observable ultrastructural changes are seen within the nucleus and consist of chromatin condensation and the enlargement of the nuclear surface. Thereafter, VDC induces morphological signs of unbalanced cellular growth, whereas TDC and cis-diamminedichloroplatinum (II) cause the development of necroses of the tumor cells, the phagocytosis of the damaged cells by macrophages, and, in consequence, complete tumor regression. Some hours after application of TDC, the formation of type-A-virus particles can be recognized. It is supposed that the apparent virus induction acts as a fortifying factor in the course of tumor inhibition by TDC. (Author abstract) (27 Refs)

92. CHANGES OF HEPATOCYTE PROLIFERATION IN MOUSE LIVER AND ADENOMATOUS NODULES DURING CCL4-INDUCED CARCINOGENESIS.

Faktor VM, Poltoranina VS, Uryvaeva IV
Lab. Cytology, N. K. Kol'tsov Inst. Biology Development, Moscow, USSR
Biull Eksp Biol Med; 93(4):79-82 1982

The effect of CCl4-induced carcinogenesis on hepatocyte proliferation was studied in SWR mice. Development of liver necrosis and foci of nodular proliferation was associated with marked decrease of the ploidy and the increase of the incidence of chromosome aberrations. These findings indicate that the early stages of liver carcinogenesis are characterized by the impairment of the mechanism of mitotic polyploidization. (13 Refs) (In RUS)

93. RESPONSES OF AMPHIBIAN EMBRYOS AND BLASTOMERES TO A TUMOR-PROMOTING PHORBOL ESTER.

Ellinger MS
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Cancer Res; 42(7):2804-2812 1982

Phorbol ester tumor promoters such as 12-O-tetradecanoylphorbol-13-acetate (TPA) alter the morphology and differentiated states of numerous cell types in vitro. It is likely that these molecules are teratogenic for vertebrate embryos in which cytodifferentiation, cell tissue interactions, and cellular motility are prominent. By examining embryonic effects, I thought that insights into mechanisms might be gained that would not be apparent in adult tissues. The purpose of this study was to characterize the responses of frog (Bombina orientalis) embryos and embryonic cells to TPA. Effects of 10 to 100 ng TPA per ml on whole embryos included epithelial dissociation, inhibition of muscle segment histogenesis and adhesive organ differentiation, and acceleration of cell sheet movements during gastrulation. Possibly correlated with accelerated gastrulation, TPA also induced circumferential rotations of lobopodial blebs in blastula cells cultured on plastic. This capacity is normally not seen until later developmental stages and is most prominent in areas undergoing morphogenetic movements. For blastula cells cultured on agar, TPA (1.0 to 10 ng/ml) inhibited cytokinesis but not karyokinesis, leading to the formation of abnormal multipolar spindles. A similar uncoupling of cytokinesis and karyokinesis in adult tissues could lead to mitotic aneuploidy, possibly an important step in tumor promotion. The amphibian embryo should be a useful organism for further studies on phorbol ester tumor promoters. (Author abstract) (49 Refs)

94. NEUROBLAST OF THE GRASSHOPPER EMBRYO AS A NEW MUTAGEN TEST SYSTEM. II. CHROMOSOME BREAKAGE INDUCED BY IN VITRO EXPOSURE OF EMBRYOS TO THE DIRECT-ACTING MUTAGENS 4NQO, MMNG, ADRIAMYCIN, AND BLEOMYCIN.

Liang JC, Gaulden ME
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Environ Mutagen; 4(3):279-290 1982

Embryos of the grasshopper Chortophaga viridifasciata (De Geer) were used in a new mutagen test system at a stage equivalent to 14-day development at room temperature. Embryos were separated from yolk and put in 35 mm x 10 mm plastic petri dishes which contained 5 ml of Mark's M-20 culture medium with 7.5% fetal calf serum plus antibiotics. Adriamycin (ADM) and bleomycin (BLM) were added to the medium directly; 4-nitroquinoline-1-oxide (4NQO) and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) were dissolved in dimethyl sulfoxide (DMSO). The dose response for the induction of acentric chromosome fragments was determined in neuroblasts of the embryos exposed in vitro to the four direct-acting chemicals, which are known to be mutagenic. After 1-hr exposure followed by a 3-hr recovery period (untreated cell cycle time is 4 hr) acentric fragments were observed at doses down to 1.0 uM 4NQO, 1.25 uM MNNG, and 0.125 uM ADM and BLM. With 4NQO, acentric fragments were induced at a dose as low as 0.125 uM after 8-hr continuous exposure. No chromosome aberrations or mitotic effects were observed in untreated embryos or those exposed only to DMSO. Comparison with other clastogen test systems currently used indicate that the grasshopper neuroblast test is the fastest and that it detects some agents that some other systems do not. (40 Refs)

GENERAL REVIEWS

95. LEUKAEMIA: A SERIES OF WORKSHOPS ON THE BIOLOGY OF HUMAN CANCER. REPORT NO. 14.

Warner NL, Metcalf D
No affiliation given
UICC Tech Rep Ser 61: 232 pp., 1981.

The biological basis of leukemia is discussed under the following headings: hemopoietic cell proliferation and differentiation (multipotential hemopoietic stem cells, progenitor cells, morphologically recognizable cells, control of differentiation and proliferation, and analysis of normal and malignant hemopoietic cell differentiation), clinical nature and classification of human leukemia (surface marker characterization, acute leukemia, chronic leukemia, and abnormal physiology), chromosomal and clonal analysis of leukemia (chromosome changes in leukemia and clonal nature of leukemia), etiology of leukemia (radiation and leukemia, induction of leukemia by chemical carcinogens, retroviruses and leukemogenesis, other etiological factors in leukemogenesis, and epidemiological patterns of leukemia), and regulation of leukemic cell growth (leukemic cell growth in vitro, regulatory control of myeloid leukemic cells, and marrow transplantation). (581 Refs)

96. CHRONIC GRANULOCYTIC LEUKAEMIA.

Shaw MT
Univ. New Mexico, Las Cruces, NM, 88001
Chronic Granulocytic Leukaemia. Eastbourne, East Sussex, England, Praeger Publishers, 251 pp., 1982.

Etiology and epidemiology of chronic granulocytic leukemia (CGL); target cells, differentiation, and clonal evolution in CGL as a model for understanding the biology of malignancy; chromosomal abnormalities; kinetics and cell function; clinical and hematologic features of CGL in the chronic phase; clinical and hematological manifestations of the terminal phase; treatment of CGL; relationship of CGL to other myeloproliferative disorders; and the Philadelphia-chromosome-negative chronic myeloid leukemias are discussed. Studies in monozygotic twins showed that CGL is an acquired disease. The monoclonality has been demonstrated by means of work with the enzyme glucose-6-phosphate dehydrogenase. Chromosome studies have revealed that not only is the Philadelphia chromosome (Ph1) number 22 and not number 21, and not only is the long arm deleted, but also a translocation of the long arm to chromosome 9 exists in most instances. Heterogeneity of the Ph1 chromosome may also occur occasionally with various other translocations. The disease known as 'Ph1-negative CGL' probably consists of several different entities. Several patients with Ph1-positive acute leukemia presenting da novo have been observed. When compared with Ph1-negative acute leukemic patients, the prognosis is poorer. The median survival time of patients with CGL has not changed markedly. The chronic phase can be controlled relatively easily with drugs such as busulfan, and a small portion of patients in the blastic phase of the disease may be treated with relatively good, but short-lived, results with prednisone and vincristine. Patients responding to the treatment usually have blast cells with the cytomorphology of lymphoblasts containing the enzyme terminal deoxynucleotidyl transferase. (1029 Refs)

97. CHROMOSOMAL ABERRATIONS IN CHRONIC B-CELL LYMPHOCYTIC LEUKEMIA.

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Cancer Genet Cytogenet; 6(2):171-181 1982

Production, incidence, and types of chromosome aberrations in chronic B-cell lymphocytic leukemia (B-CLL) are reviewed. Of polyclonal B-cell mitogens, Epstein-Barr virus and lipopolysaccharide from E coli have been the most successful for cytogenetic analysis of B-CLL. The mitogenic responses measured by 3H-labeled thymidine incorporation into leukemic cells and the mitotic index are variable. Difficulties associated with calculating reliable incidence figures for chromosomal aberrations in B-CLL are considered. In B-CLL, both numerical and structural aberrations are found. The most common numerical aberration is an extra chromosome 12. Other aberrations include deletion of chromosome 14, translocations, deletions, and other extra chromosomes. Many of the chromosomal abnormalities seen in B-CLL have also been found in other malignant hematopoietic disorders, particularly lymphoproliferative disorders. However, the most common abnormality, the extra chromosome 12, is rare in other disorders. The biological significance and prognostic importance of chromosomal aberrations in B-CLL are discussed. (72 Refs)

98. THE CHROMOSOMAL EFFECTS OF THE ORAL CONTRACEPTIVE.

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J Surg Oncol; 20(2):115-118 1982

A general review of reports on the chromosomal effects of oral contraceptive has been undertaken, and it is quite apparent that there is a scarcity of literature on these very important investigations. Also, those that have been undertaken, cannot be properly assessed on account of, one supposes, subjects' background and lack of numbers, differences in techniques and, above all, the small number of metaphases analyzed. Apart from the report by Mills and colleagues, none of the reports mentioned exogenous agents to which the subjects might have been exposed, especially in cases where there has been an increased frequency of chromosomal aberrations. All these considerations must be taken into account for, as yet, the reports are too conflicting to 'indict' the oral contraceptive as having chromosome-breaking properties. (Author abstract) (22 Refs)

99. INTRINSIC RADIOSENSITIVITY OF PROLIFERATING MAMMALIAN CELLS.

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Dept. Radiobiology and Health Protection, Inst. Nuclear Res., 03-195 Warsaw, Poland

Adv Radiat Biol; 9:281-321 1981

Radiation target(s), DNA repair, organization of chromatin, endogenous radiomodifiers, water content and 'structure', cellular recovery from potentially lethal and sublethal damage, and membrane-dependent factors are discussed. Factors determining intrinsic radiosensitivity at the molecular level fall into two categories: factors that alter the quantity of lesions produced in DNA, and factors that are responsible for the interaction of lesions, their accessibility to repair, energy supply, and activity of repair enzymes. (247 Refs)

100. MECHANISMS FOR CHROMOSOMAL ABERRATIONS IN MAMMALIAN CELLS.

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Mutat Res; 95(1):1-6 1982

Lesions responsible for chromosomal aberrations (CA) induced by ionizing radiations, role of base damage in x-ray-induced CA, and experiments involving repair inhibitors are discussed. The frequencies of DNA-double strand breaks induced by x-rays alone, as well as in combination with Neurospora crassa endonuclease (NE) were measured by neutral sucrose-gradient centrifugation analysis to confirm the cytological findings and their interpretation. X-irradiation of CHO cells with 30 kilorad led to 8.8 double-strand breaks/10(10) dalton of DNA, and post treatment of the cells with NE led to a doubling of the frequencies of double-strand breaks induced by x-rays supporting the conclusion that DNA double-strand breaks are the most probable lesions that lead to the formation of CA induced by ionizing radiations. When G0 or G1 cells from patients with ataxia telangiectasia were irradiated with x-rays, both chromosome and chromatid types of aberration were obtained in contrast to mainly chromosome-type aberrations obtained in normal cells. Several inhibitors of DNA synthesis, such as cytosine arabinoside, aphidicolin, and hydroxyurea, as well as inhibitors of poly(ADP-ribose) polymerase (PRP), have been used in x-ray experiments involving human peripheral blood lymphocytes. When human peripheral blood lymphocytes were irradiated and post treated with inhibitors of PRP, such as 3-aminobenzamide, for at least 6 hr prior to stimulation, a doubling of the frequency of aberrations was observed. The results supported the conclusion that DNA double-strand breaks are the most important lesions responsible for radiation-induced CA. (19 Refs)

101. PREDICTIVE ASSAYS FOR MUTAGENS AND CARCINOGENS.

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Scientific Considerations in Monitoring and Evaluating Toxicological Research. Gralla EJ, ed. Washington, D. C., Hemisphere Publishing Corporation, 221 pp., 1981.

General principles involved in the formulation of a testing program for mutagens and carcinogens and the evaluation of results are presented. Considerations in the selection of systems and evaluation of results are outlined for bacterial mutagenesis assays, mammalian cell culture mutagenesis assay, cell transformation assays, DNA damage assays, DNA repair assays, and whole-animal systems including classical cytogenetic techniques, sister chromatid exchange assays, dominant lethal assay, sperm morphology assay, and the recessive spot test. (22 Refs)

102. RELATIONSHIP OF DNA TERTIARY AND QUATERNARY STRUCTURE TO CARCINOGENIC PROCESSES.

Lipetz PD, Galsky AG, Stephens RE
Dept. Radiology, Ohio State Univ., Columbus, OH, 43210
Adv Cancer Res; 36:165-210 1982

DNA superstructure as studied in nucleoids (permeabilized and protein-depleted nuclei) and possible correlations between modification of the tertiary (supercoiling) and quaternary (supercoiled domains) levels of organization and carcinogenic processes are reviewed. Evidence that the nucleoid technique can be used to quantify extremely low levels of DNA strand breaks (less than 1/4.4 x 10(10) daltons of DNA) is discussed. Chromatin origins of DNA supercoiling; physiological relevance of decreased nucleoid DNA supercoiling; novobiocin and nalidixic acid as probes of DNA supercoiling; prokaryotic DNA supercoiling; and eukaryotic DNA superstructure are discussed. Crown gall tumorigenesis, chronic lymphocytic leukemia, 12-O-tetradecanoyl-phorbol-13-acetate-induced alterations of DNA superstructure in normal human cells and chromatin damage and repair are addressed. The relationship of DNA superstructure to the processes of carcinogenesis, carcinogenic promotion, and Z DNA is discussed. DNA superstructure studies may lead to a resolution of the conflict between the idea that neoplastic transformation results from altered informational flow from DNA (as in somatic mutation) and the concept that membrane-associated events lead to malignant transformation. DNA superstructure could be responsive to both levels of control. (211 Refs)

103. GUIDELINES FOR STUDIES OF HUMAN POPULATIONS EXPOSED TO MUTAGENIC AND REPRODUCTIVE HAZARDS. PROCEEDINGS OF A CONFERENCE HELD IN WASHINGTON, D. C., 26-27 JANUARY, 1981.

Bloom AD
Dept. Pediatrics and Human Genetics and Development, Coll. Physicians and Surgeons, Columbia Univ., New York, NY
Guidelines for Studies of Human Populations Exposed to Mutagenic and Reproductive Hazards, Proceedings of a Conference held in Washington, D. C., 26-27 January, 1981. White Plains, NY, March of Dimes Birth Defects Foundation, 163 pp., 1981.

Panels were established to study cytogenetic effects of genotoxic chemicals on human populations, reproductive effects of genotoxic chemicals, and testing for mutagens in human populations. Discussion of cytogenetic study guidelines included presentation of background information, methods for study of induced chromosomal aberrations, analysis and classification of chromosomal structural changes, analysis of data on structural aberrations, methods and procedures for analysis of sister chromatid exchange (SCE) in human lymphocytes, and significance of aberrations and SCE. Reproductive study guidelines are considered in relation to indices of reproductive failure, statistical issues, guidelines for Level I activities (accessible sources), decision making (moving from Level I to Level II), long-term follow-up studies (Level III), and data on selected end points. Topics discussed with regard to detection of gene mutation and DNA damage in the human population included the following: background information, the need for genetic monitoring, criteria for defining a human population at risk, methods potentially useful for evaluating human populations exposed to mutagenic hazards, and current status of the use of mutation assays to evaluate human populations. Implementation of the guidelines must consider cost of inadequate evaluations of potential mutagens and teratogens, coordination of the three sets of guidelines, and statistical concerns. (384 Refs)

104. MEETING REPORT: WORKSHOP ON THE PRACTICAL APPLICATION OF THE MAMMALIAN SPOT TEST IN ROUTINE MUTAGENICITY TESTING OF DRUGS AND OTHER CHEMICALS.

Braun R, Russell LB, Schoneich J
Zentralinstitut fur Genetik und Kulturpflanzenforschung der AdW der DDR, 4325 Gatersleben, E. Germany
Mutat Res; 97(2):155-161 1982

The mammalian spot test, which was developed in relation to radiation mutagenesis, is reviewed with respect to treatment procedure, spot classification, statistical evaluation, and interpretation of results. Variables regarding treatment include time, dose, and route of application. Spots resulting from expression of recessives (RS), from cell killing (WMVS), and spots due to misdifferentiation (MDS) are distinguishable by location and color, and must be recorded separately. The spots test is relatively fast compared with some other whole-mammal tests, but requires more resources than do assays involving prokaryotes, lower eukaryotes and cell-culture systems. Major strengths of the spot test are it is an in vivo test; it monitors gene mutation end-points, as well as several types of chromosomal damage; and it provides ancillary information on cytotoxicity, embryotoxicity and teratogenicity of a compound. A positive result classifies a chemical as a potential carcinogen; to date all agents found positive have been carcinogens or have not been tested for carcinogenicity. A positive spot test will also indicate the possibility that inherited damage could be produced, which would indicate further germ-line mutagenicity studies. A negative test must be qualified by the possibility of a placental barrier. (3 Refs)

105. EXPRESSION OF EUKARYOTIC VIRAL AND CELLULAR GENES.

Pettersson RF, Kaariainen L, Soderlund H, Oker-Blom N
Dept. Virology, Univ. Helsinki, Helsinki, Finland
Expression of Eukaryotic Viral and Cellular Genes. London, Academic Press, 324 pp., 1981.

Recent advances in molecular virology, molecular genetics, and recombinant DNA research are combined in a discussion of expression of eukaryotic viral and cellular genes. Structure and expression of DNA virus genes are reviewed with respect to molecular analysis of adenovirus transformation, control of adenovirus messenger (m)RNA production by differential transcription and differential stability of mRNA, an early adenovirus glycoprotein and its association with transplantation antigens, the control of adenovirus early gene expression, and mutational analysis of regulatory elements of simian virus 40. Retrovirus genes are discussed with respect to OK 10 virus-transformed bone-marrow-derived cell line, the transforming insert in the Abelson murine leukemia virus genome, and DNA intermediates in the replication of retroviruses. RNA virus genes are discussed with respect to the genome of single-stranded messenger-sense RNA viruses, influenza virus, capped cellular RNAs, drift and shift of influenza A-type virus, vesicular stomatitis virus and host cell phosphoproteins, initiation of eukaryotic protein synthesis, alphavirus gene products, Semliki Forest virus, RNA containing heterogeneous 5'-terminal nucleotide sequences, and Semliki Forest virus defective interfering RNA using DNA copies. Eukaryotic genes are discussed with respect to structure, organization and developmental expression of chorion multigene families, gene amplification and methotrexate resistance, RNA-protein complexes precipitated by Lupus antibodies, promoter sequences, expression of cloned eukaryotic genes in microorganisms, human genomic DNA-encoding Pro-opiomelanocortin, and functional yeast minichromosomes containing centromeric DNA. (701 Refs)

OTHER RELATED STUDIES

106. DNA-REPAIR DEFICIENCIES DO NOT AFFECT INTERCALATOR-INDUCED CYTOTOXICITY OR DNA SCISSION IN HUMAN CELLS.

Zwelling LA, Mattern MR
Building 37, Room 5D17, 9000 Rockville Pike, Bethesda, MD, 20205
Mutat Res; 104(4/5):295-304 1982

Toxicity of the DNA intercalator 4'-(acridinylamino)-methanesulfon-m-aniside (m-AMSA) was compared to the toxicity of xeroderma pigmentosum (XP) and ataxia telangiectasia (A-T) cells, and normal human fibroblasts and the protein associated DNA-strand breaks produced by m-AMSA are discussed. The efficiency of m-AMSA in reducing colony-forming ability was the same in all three human fibroblast lines. Quantification of m-AMSA production of DNA-strand breaks by alkaline elution also revealed no differences among the three lines. Results differed from those of experiments which measured cytotoxic effect and DNA-strand breaks produced by damaging agents. Scission produced by m-AMSA also disappeared similarly in normal, XP, and A-T lines. The m-AMSA breaks in all three cell lines were associated with comparable magnitudes of DNA-protein crosslinking. The concentration of m-AMSA associated with each cell type was measured by the use of radioactive compound. The normal cells displayed no reduction in either m-AMSA sensitivity or single-strand break production. A true increased sensitivity of the variant cells thus was not masked by deficient m-AMSA uptake. The effects upon DNA biochemistry and cell survival produced by m-AMSA appeared to be mediated by cellular factors other than those that are deficient in human cell lines abnormally sensitive to other DNA-reactive agents. (31 Refs)

107. CLONAL GROWTH OF CARCINOGEN-INDUCED ENZYME-DEFICIENT PRENEOPLASTIC CELL POPULATIONS IN MOUSE LIVER.

Rabes HM, Bucher T, Hartmann A, Linke I, Dunnwald M
Pathologisches Institut, Universitat Munchen, Munich 2, W. Germany
Cancer Res; 42(8):3220-3227 1982

The cellular origin of preneoplastic subpopulations in liver during chemical carcinogenesis has not yet been clarified. An experimental approach to this problem became possible by using female phenotypic mosaics caused by the X-chromosome inactivation ('lyonization') occurring early in embryogenesis. Allozymes of the X-linked enzyme phosphoglycerate kinase (PGK-1) served as markers of the maternal (wild-type PGK-1B) and paternal (variant PGK-1A) X-chromosomes in crosses of near-congenic C3H mice. These PGK allozymes are of similar activity and stability but can be separated electrophoretically and quantified by a fluorimetric method. Pgk-1a/Pgk-1b heterozygous females were subjected to chronic 2-acetylaminofluorene feeding for up to 14 mo. Phenotypic expression of PGK-1B and PGK-1A was determined in ug samples as well as in mg samples of liver and other organs. Samples of adenosine triphosphatase-deficient preneoplastic populations punched out from cryostat serial sections of liver of 2-acetylaminofluorene-fed mice disclosed a PGK allozyme pattern strikingly different from the norm. Thirty-nine of 40 preneoplastic nodules contained a pure population of either PGK-1A or PGK-1B expressing cells. Mean contamination by the opposite PGK type was 1.1%. In all cases, the PGK expression in the preneoplastic nodules differed from the surrounding liver parenchyma. Only a single large hyperplastic nodule was composed of several subpopulations with respect to PGK expression. Determination in normal liver tissue of the patch size of coherent populations with a homogeneous expression of one PGK allozyme revealed an av of about eight hepatocytes per patch. Each microsample used for PGK determinations consisted of an av of 25 patches. It is evident from these results that AAF-induced, ATPase-deficient preneoplastic subpopulations in the mouse liver are in all probability clones derived from a single cell. (Author abstract) (43 Refs)

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CLINICAL STUDIES OF CHROMOSOMES IN HUMAN CANCER

1. BREAK POINTS IN CHROMOSOME 1 ABNORMALITIES OF 218 HUMAN NEOPLASMS.

Brito-Babapulle V, Atkin NB
(c/o Atkin) Dept. Cancer Res., Mount Vernon Hosp., Northwood, Middlesex HA6 2RN, England
Cancer Genet Cytogenet; 4(3):215-225 1981

A survey of 343 break points that lead to chromosome number 1 abnormalities in 218 human neoplasms showed that 49.9% were located in or immediately adjacent to the centromeric heterochromatin. Amongst rearrangements with breaks in bands p12-q21 were 27 isochromosomes, 22 translocations of the long arm, and four translocations of the short arm to the heterochromatic regions of other chromsomes, and 35 deletions resulting in chromosomes consisting mainly or solely of one arm. Deletions following breakage at various sites in the short arm of chromosome number 1 are frequent in malignancies and are quite often found in cells that are trisomic for the long arm. It is suggested that fragility of chromosomes generated as a result of early events in carcinogenesis may be one source of

HE 20.3173/2:

chromosome rearrangements, including those of chromosome number 1, on which selection can operate and give rise to progressively more malignant clones. (Author abstract) (79 Refs)

2. CLINICAL SIGNIFICANCE OF CLONAL CHROMOSOME CHANGES IN LEUKEMIC LYMPHOCYTES OF CHRONIC LYMPHOCYTIC LEUKEMIA (MEETING ABSTRACT).

Han T, Ozer H, Sadamori N, Gagera R, Gomez G, Henderson ES, Minowada J, Sanberg AA
Roswell Park Memorial Institute, Buffalo, New York, 14263
Proc Am Soc Clin Oncol; 1:C-723 1982

Recently it has become possible to induce leukemic B lymphocytes from patients with chronic lymphocytic leukemia (CLL) into mitosis by polyclonal B-cell activators such as Epstein-Barr virus (EBV), Escherichia coli lipopolysaccharide (LPS), protein A, tetradecanoyl-O-phorbol-13-acetate (TPA) and pokeweed mitogen (PWM). In the present study, adequate metaphases of leukemic cells stimulated by these B-cell activators for cytogenetic analysis were obtained in 49 of 60 CLL patients. Nineteen of 49 patients had clonal chromosome changes in the leukemic cells. Similar chromosome abnormalities were detected with more than two kinds of mitogen, suggesting that these changes are not produced by the mitogenic agents. Clonal chromosome changes were seen not only in treated patients but also in untreated patients, indicating that the changes are not induced by chemotherapeutic agents. The most common types were trisomy 12, trisomy 16, trisomy 18 and Ph1-like chromosomes. Fifteen of 31 active patients had chromosome changes whereas only four of 18 patients in complete or partial remission were abnormal. Eleven of 16 patients with Stage III and IV, but only eight of 33 patients with Stage 0-II had chromosome changes. A higher incidence of abnormalities was observed in patients with either monoclonal spikes or hypogammaglobulinemia and marked lymphoctosis than in those with normal immunoglobulins and mild to moderate lymphocytosis, respectively. There was no correlation between the chromosome abnormality and sex, age, disease duration, treatment status or leukemic phenotype. (no Refs)

3. OBSERVATIONS ON CHROMOSOMES OF 18 CASES OF ACUTE LEUKEMIA.

Cao J, Shen B, Xu J, Ding Y
Dept. Hematology, Shanghai Sixth People's Hosp., Shanghai, People's Republic of China
Zhonghua Xueyexue Zazhi; 2(3):166-169 1981

Results of chromosome studies are described for 18 patients (12 males, 6 females; 2-69 yr old). Ten cases were lymphocytic acute leukemia, 4 were acute granulocytic and 2 acute monocytic leukemias. Patients were treated with combination chemotherapy which consisted of different protocols. Examination of bone marrow chromosomes revealed a definite relationship between chromosomal changes and treatment efficacy as well as prognosis. (6 Refs) (In CHI)

4. CHROMOSOMAL FINDINGS AND THEIR CORRELATION TO PROGNOSIS IN ACUTE LYMPHOCYTIC LEUKEMIA.

Kaneko Y, Hayashi Y, Sakurai M
(c/o Sakurai), Saitama Cancer Center, 818 Komuro, Ina, Saitama 362, Japan
Cancer Genet Cytogenet; 4(3):227-235 1981

Sixteen of the 17 patients with acute lymphocytic leukemia (ALL) were revealed to have chromosome abnormalities in their leukemic cells. Of nine children, six had modal chromosome numbers between 50 and 59; these patients and one additional patient with a pseudodiploid karyotype have achieved and retained a complete remission. The only patient without chromosome abnormalities achieved a remission, but had a relapse and died. The only child who expired without achieving a remission had 47 chromosomes in his leukemic cells. Of eight adults, none had the hyperdiploidy seen in the children. The four with hypo- or pseudodiploidy failed to achieve a complete remission. One patient had 47 chromosomes in his leukemic cells, and this patient and the remaining three, all with ploidy abnormalities, achieved a complete remission, but a relapse occurred and they died. The chromosomal abnormalities were very extensive in most cases, many patients having marker chromosomes of an unknown origin. Four patients clearly exhibited karyotypic evolution when they relapsed. The patients with hyperdiploidy had a better prognosis, and those with pseudodiploidy had a poorer prognosis. The role of individual chromosome aberrations, however, remains to be elucidated. (Author abstract) (27 Refs)

5. NEAR-HAPLOID CHROMOSOME NUMBERS IN LEUKEMIA: SIGNIFICANCE TO LEUKEMOGENESIS (MEETING ABSTRACT).

Chaganti RS
Laboratory of Cancer Genetics and Cytogenetics, Memorial-Sloan-Kettering, Cancer Center New York, NY, 10021
Am J Hum Gen; 33(6):61A 1982

Chromosome numbers in most leukemias, when abnormal, cluster around either the diploid (hypo or hyper) or tetraploid (hypo to hyper) modes arising through non-disjunction and endoreduplication. Marker chromosomes also often characterize leukemic cells. Extremely rare instances of severe hypodiploidy have been reported in acute lymphoblastic leukemia (ALL) and in blastic phase chronic myelogenous leukemia. We report three cases of ALL with near haploid chromosome numbers. These along with three other cases reported in the literature comprise a new cytogenetic entity among ALL. Our patients number 1 and 2 were 7-year-old and 18-year-old males, while patient number 3 was a 16-year-old male. The leukemic marrow clones of the three patients exhibited 24, 26, and 28 chromosomes, respectively. In each case, a complete haploid set of autosomes and both sex chromosomes were present. In addition, chromosomes number 14 and 21 in the case of patient number 2 and chromosomes number 6, 10 and 21 in the case of patient number 3 were present in two copies. Rearrangements were absent. This cytogenetic picture suggests derivation by either non-disjunction and chromosome elimination or by a form of reductional division restricted to autosomes with subsequent restoration of disomy of some chromosomes through non-disjunction. (no Refs)

6. PROGNOSIS IN ACUTE MYELOCYTIC LEUKEMIA (AML) WITH T(8 ; 21) TRANSLOCATION (MEETING ABSTRACT).

Cramer P, Bernheim A, Daniel MT, Berger R, Flandrin G, Auclerc MF, Weil M, Marty M, Boiron M
Service d'hematologie, Hopital Saint Louis, Paris, France
Proc Am Soc Clin Oncol; 1:C-745 1982

Thirteen previously untreated patients with AML and t(8;21) translocation were observed in our institution between November 1978 and October 1981; using the criteria of the FAB classification these patients were all in class M2 and they all had a characteristic cytologic picture consisting essentially of large myeloblasts with an abundant cytoplasm containing a large Auer rod; t(8;21) translocation was associated with the loss of a sex chromosome in 9 cases out of 13; some cells with a normal karyotype were observed in 11 out of the 13 patients studied. The 13 patients ranged in age from 5 to 51 years (median age 15); there were 8 male and 5 female patients; initial white blood cells count ranged from 2,6000 to 44,500 (median 9,300); the 13 patients had a complete remission (CR); 7 with one course of therapy 6 requiring 2 courses; remission was induced by cytarabine and one anthracycline (daunorubicin or zorubicin) associated with other drugs in 8 patients (6-mercaptopurine and mitoguazone for 4, vincristine and prednisone for 3 and cyclophosphamide for 1); the 13 patients all had a maintenance chemotherapy with pulses every four to five weeks. The median duration of CR is projected to be 11.5 months; the probability that the patients will remain in CR is 21.9% at 24 months. These results are not statistically different from the results we observed in a group of 123 patients with AML (M1, M2, m4) and comparable initial clinical characteristics who have been treated with the same treatment in our institution. (no Refs)

7. NEW CYTOGENETICS FINDINGS IN A PATIENT WITH ACUTE PROMYELOCYTIC LEUKEMIA (APL) (MEETING ABSTRACT).

Rodriguez S, Verma RS, Dosik H
Department of Medicine, The Jewish Hospital and Medical Center of Brooklyn, Brooklyn, NY
Am J Hum Gen; 33(6):67A 1982

Besides the clinical and morphological features, a specific association with a unique chromosome translocation t(15q+;17q-) is recognized in patients with acute promyelocytic leukemia (APL). We present a case where chromosomal abnormalities are not distinctive for APL. A 19 year old male was diagnosed as having APL. Complete blood count on admission showed hemoglobin 16.6 gm/dl; hematocrit 48%, platelets 133 x 10(9)/liter; and white cells, 4100/mm3, with a differential of 7% blasts, 32 promyelocytes, 4% myelocytes, 13% granulocytes, 8% monocytes, 36% lymphocytes. A bone marrow aspiration was done which showed blasts 10% promyelocytes 72%, granulocytes 12%, lymphocytes 2%, erythroid precursors 2% and plasma cells 2%. It is necessary to review the morphological features of all cases of APL and compare them with chromosomal changes. Cytogenetic analysis was performed on 12/11/80 and three consistent markers were found: M1(t(11q;1q)), M2(t(6p;13q)), M3(i(17q)) with the loss of Y chromosome from his bone marrow aspirate. Ninety percent cells were abnormal while 10% of the cells were cytogenetically normal. A second aspirate was done on 3/2/81 and the same three markers were noted. However, both chromosome number 1s were normal, suggesting a secondary cytogenetic change in the patient. (no Refs)

8. CHROMOSOME PATTERN, OCCUPATION, AND CLINICAL FEATURES IN PATIENTS WITH ACUTE NONLYMPHOCYTIC LEUKEMIA.

Mitelman F, Nilsson PG, Brandt L, Alimena G, Gastaldi R, Dallapiccola B
Dept. Clinical Genetics, Univ. Hosp., S-221 85 Lund, Sweden
Cancer Genet Cytogenet; 4(3):197-214 1981

Chromosome banding pattern of bone marrow cells, cell morphology according to the FAB classification, and clinical findings were compared in two groups of adult patients with acute nonlymphocytic leukemia (ANLL): 52 patients occupationally exposed to chemical solvents, insecticides, or petrol products, and 110 patients with no history of occupational exposure to potential mutagenic/carcinogenic agents. Striking differences were found between the two groups: (1) Clonal chromosomal aberrations were present in 75% of exposed patients compared with only 32% in the nonexposed group. (2) Of the patients exposed to solvents and insecticides 92% had abnormal chromosomes, wheres only 29% of patients exposed to petrol products showed abnormalities; in the total material 10/13 exposed patients with normal chromosomes were exposed to petrol products. (3) The relationship between chromosomal abnormality and exposure was evident in both females and males. However, only 29% of women with an abnormal karyotype were exposed, whereas 70% of males with an abnormal karyotype were exposed. (4) The incidence of certain characteristic karyotypic abnormalities, ie,-5/5q-,-7/71-, +8, +21, t(8;21), and t(9;22), were decidedly more common in exposed than in nonexposed patients. At least one of these changes were present in 92% of exposed patients with aberrations, whereas in the nonexposed group the incidence was only 60%. (5) The monocytic varieties of ANLL (M4 + M5) were more common in the nonexposed patients, whereas erythroleukemia (M6) was more common in the exposed group. The predominance of abnormal karyotypes in the exposed compared to the nonexposed patients was similar in leukemia types M1 + M2 and in M4 + M5. (6) There was no difference in survival time between the two groups and the same correlation was obvious in both exposed and nonexposed patients: patients who had only abnormal metaphases had poorer prognosis than those with normal bone marrow metaphases only (6 vs 1.5 mo). This correlation was obvious in patients classified as acute myeloid leukemia (AML) as well as in the monocytic varieties of ANLL. (Author abstract) (36 Refs)

9. ALLOGENEIC MARROW TRANSPLANTATION FOR ACUTE NON-LYMPHOBLASTIC LEUKEMIA IN RELAPSE USING FRACTIONATED TOTAL BODY IRRADIATION.

Buckner CD, Clift RA, Thomas ED, Sanders JE, Stewart PS, Storb R, Sullivan KM, Hackman R
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Leuk Res; 6(3):389-394 1982

Twenty-three patients (10-52 yr old) with acute non-lymphoblastic leukemia in relapse were treated with cyclophosphamide (60 mg/kg on days-10 and-9), fractionated total body irradiation (200 rad/day on day-5 and day 0), and allogeneic marrow transplantation. One patient died of infection on day 17 without evidence of engraftment; all other patients achieved engraftment. Eight patients relapsed between 30 and 619 days after transplantation and died of leukemia-related problems. Six of the 23 patients (26%) were alive and free of disease 756-1,306 days following transplantation. Seven of the 22 patients with sustained engraftment developed significant acute graft-vs-host disease (GVHD, Grade 2 or greater). Eight of 15 patients surviving greater than 100 days developed chronic GVHD. Of 11 with sustained engraftment and no significant GVHD, none survived. Sixteen patients had cytogenetic studies of marrow prior to transplantation to detect leukemia-associated chromosomal abnormalities. In 2 patients such abnormalities could not be detected, and a variety of chromosomal rearrangements was present in the 14 other patients. All eight patients who relapsed after transplantation had leukemia-associated chromosomal markers before transplantation, and four of the patients had donors of opposite sex. After relapse, five patients were studied, and in all patients the recurrent leukemia cells were of host type. (23 Refs)

10. ACUTE LEUKEMIA FOLLOWING A MALIGNANT TERATOMA IN A CHILD WITH KLINEFELTER'S SYNDROME. CASE REPORT AND REVIEW OF SECONDARY LEUKEMIAS IN CHILDREN FOLLOWING TREATMENT OF A PRIMARY NEOPLASM.

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Cancer; 50(4):684-689 1982

A case of Klinefelter's syndrome with the development of a mediastinal teratocarcinoma is reported suggesting that the association of a gonadotropin-secreting tumor with the XXY chromosomal abnormality may be more than coincidental. Whereas the child appeared to survive the effects of the teratocarcinoma, he succumbed to acute leukemia 2 yr later. This prompted a review of secondary leukemias in children following chemotherapy/radiotherapy for another primary malignancy. These patients responded poorly to treatment of the secondary leukemia with a median survival of about 4 mo. The incidence of secondary leukemias might be expected to be on the rise as increasing numbers of pediatric cancer patients are surviving longer after treatment with agents that are potentially leukemogenic or carcinogenic themselves. Children who have survived cancer and its therapy present special problems and it will be necessary for the pediatrician and practitioner to monitor these children. (Author abstract) (47 Refs)

11. KARYOTYPE STABILITY IN THE PRIMARY TUMOR AND MULTIPLE METASTASES OF A HUMAN MELANOMA (MEETING ABSTRACT).

Balaban G, Herlyn M, Guerry D, Nowell P

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Proc Am Assoc Cancer Res; 23:130 1982

Previous data on human melanoma chromosomes have been from metastases and/or cells cultured for long periods. We studied direct preparations or early passages of a primary nodular malignant melanoma and five cutaneous metastases removed over 18 months. The patient had local radiation to other sites but no chemotherapy. Karyotypes of the primary tumor were bimodal: 10% with a mode of 43 chromosomes; 90% with a mode of 85 chromosomes. Both cell populations had polysomy for chromosome 7, and three abnormal marker chromosomes: 1p+, 11p+, and 16q+. They also shared five other consistent and distinctive marker chromosomes whose origin could not be defined. The first metastasis had only the hypotetraploid cells, with the same markers. Four additional metastases all showed varying proportions of the same hypodiploid and hypotetraploid populations. There were minor karyotypic differences among all metastases examined involving gains or losses of the five undefined markers in the primary tumor. The cytogenetic data indicate that the primary lesion and metastases of this melanoma were components of the same neoplastic clone. Two related subpopulations, hypodiploid and hypotetraploid, were apparently coexisting in vivo (and during early passage in vitro) without major selective advantage for either. The abnormal karyotype, during the 18 months of study, was very stable, showing only minor variation in different lesions, suggesting little selective pressure within the host in this late stage of disease. (no Refs)

12. CHROMOSOME ANALYSIS IN 176 CASES OF VARIOUS FORMS OF PLEURAL EFFUSION.

Gallareto M, Ghiazza GF, De Giorgis L, Gabutto U

Divisione di Medicina Generale, Ospedale Civile di Acqui Terme, Acqui Terme, Italy

Arch Sci Med (Torino); 139(2):193-202 1982

Results of chromosome analysis of pleural liquid sediments from 71 patients with pleural effusions of neoplastic origin and from 105 patients with transudative or inflammatory effusions are presented. Numerical and morphological karyotype alterations indicative of the pleural effusion were found in 79% of the tumor patients and in none of the 105 patients with transudative or inflammatory effusions, even though mitoses with numerical changes (hyperdiploidy) were found in 2/105 patients. The results of the Papanicolaou tests were positive in 63%. The results of the chromosome analyses were positive in 56/71 tumor patients: Papanicolaou tests were performed 58/71 cases; they were positive in 31/56 cases with positive results of chromosome analysis and negative in 12/56. The results of the chromosome analysis were negative in 15/71 patients in 7 of which the results of the Papanicolaou test were positive. When both methods were applied it was possible to establish the diagnosis in 90% of all cases. (27 Refs) (In ITA)

13. USE OF CYTOGENETIC ANALYSIS OF BODY FLUIDS IN CANCER DIAGNOSIS.

Izadian N

Pathology Dept., Women's Hosp., Piche-Shemran, Enghelab Ave., Teheran, Iran

J R Soc Med; 75(6):435-442 1982

Direct chromosome preparations were made from 52 malignant and 21 nonmalignant effusions. An effusion was classified as malignant if 2% of the counted cells showed abnormal karyotypes. There was a significant relationship between diversified karyotypes and the pathological nature of tumors: diversity of karyotypes was much higher in undifferentiated adenocarcinoma, anaplastic carcinoma and embryonal cell carcinoma cells than in well-differentiated cancer cells. Diagnosis was positive for 38 of the 52 malignant effusions by cytological examination (73% sensitivity), and positive for 41 of the 52 by cytogenetic analysis (78% sensitivity). There were no false positive results using both cytogenetic and cytologic examinations (92% sensitivity). Particularly in patients with equivocal cytology, cytogenetic analysis appears to be a useful tool in the diagnosis of malignant effusions. (Author abstract) (22 Refs)

DNA CONTENT AND PLOIDY CHANGES

14. VARYING INVOLVEMENT OF PERIPHERAL GRANULOCYTES IN THE CLONAL ABNORMALITY -7 IN BONE MARROW CELLS IN PRELEUKEMIA SECONDARY TO TREATMENT OF OTHER MALIGNANT TUMORS: CYTOGENETIC RESULTS COMPARED WITH RESULTS OF FLOW CYTOMETRIC DNA ANALYSIS AND NEUTROPHIL CHEMOTAXIS.

Pedersen-Bjergaard J, Vindelov L, Philip P, Ruutu P, Elmgreen J, Repo H, Christensen IJ, Killmann SA, Jensen G
Dept. Internal Medicine, Finsen Inst., Strandboulevarden 49, DK-2100, Copenhagen 0, Denmark
Blood; 60(1):172-179 1982

DNA content of isolated peripheral granulocytes and mononuclear cells was determined by flow cytometry and the results correlated with neutrophil chemotaxis, in 10 patients with secondry preleukemia or overt acute leukemia and cytogenetic defects of chromosome no 7 in bone marrow cells. Nine patients had a hypodiploid clone with a missing chromosome no 7, one lacked the long arm of a chromosome no 7. The DNA content of granulocytes was normal in five of these cases and significantly reduced in four cases. In one patient, two populations of granulocytes were observed, one with a normal, the other with a reduced DNA content. In vitro chemotaxis of washed peripheral granulocytes was normal in three patients, reduced in seven patients. A relationship was observed between the cytogenetic results from the bone marrow, the DNA content of peripheral granulocytes, and the chemotactic response. Thus, four patients with a high percentage of abnormal mitoses in the marrow had a decreased DNA content in granulocytes and a reduced chemotactic response, possibly due to involvement of mature peripheral granulocytes in the leukemic clone. Conversely, three patients with a high percentage of normal bone marrow mitoses had a normal DNA content in granulocytes and a normal chemotactic response, suggesting a differentiation of granulocytes in these cases from normal bone marrow precursors. Two patients showed a decreased chemotactic response, despite a normal DNA content in all granulocytes, or in a major population of these cells. This indicates that mechanisms other than involvement of granulocytes in a leukemic clone with monosomy 7 may contribute to a decreased chemotaxis. The results confirm previous reports of decreased neutrophil chemotaxis in monosomy 7 in patients with granulocytes of a leukemic origin. We can now add a further case to two previously described cases of 7q- with decreased chemotaxis. This suggests that the long arm of chromosome no 7 could be of special importance tor neutrophil chemotaxis. (Author abstract) (29 Refs)

15. PRETREATMENT FLOW CYTOMETRY (FCM) OF DNA CONTENT IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKAEMIA (ALL) (MEETING ABSTRACT).

Look AT, Melvin S, Murphy S, Williams D, Brodeur G, Mauer A
St. Jude Children's Research Hospital, Memphis, TN, 38101
Cell Tissue Kinet; 15(1):106 1982

The cellular DNA content distributions of propidiumiodide stained bone marrow lymphoblasts from 56 consecutive untreated children with ALL were studied with FCM in order to detect aneuploidy. Aneuploidy was expressed as a DNA index (DI) (leukemia G1/0 channel number/normal G1/0 channel number), and gross chromosomal additions or deletions (+/-6 chromosomes) were required in the leukemia karyotype for detection of an abnormal DI by FCM. Patients were subdivided according to reactivity of the lymphoblasts with specific heteroantisera into undifferentiated (U), common (C) and T cell ALL. Aneuploidy was detected in 17 of 40C ALL patients. Lymphoblasts from fourteen patients had a single hyperdiploid stemline with a median DI of 1.20. Two patients had hypodiploid C ALL, one of which was near-haploid with a second clone resulting from duplication. In contrast to C ALL, aneuploidy was not evident by FCM in any of thirteen patients with T ALL. One of three patients with U ALL showed aneuploidy with a DI 2.12. In conclusion (1) FCM of cellular DNA content provided a distinctive marker of the malignant cells for some patients with C and U ALL, permitting convenient monitoring of the response to therapy, and (2) lymphoblasts with T cell differentiation did not show aberrations in DNA content by FCM. (no Refs)

16. FLOW CYTOMETRIC MEASUREMENT OF PLOIDY AND PROLIFERATIVE ACTIVITY OF CARCINOMAS OF THE OROPHARYNGEAL MUCOSA.

Grassel-Pietrusky R, Hornstein OP
Dermatologische Universitats-Klinik, Hartmannstrasse 14, D-8520 Erlangen, W. Germany
Arch Dermatol Res; 273(1/2):121-128 1982

The ploidy rate and proliferative properties of squamous cell carcinomas of the oropharyngeal and laryngeal mucosa were analyzed by flow cytophotometry. Tissue specimens were taken from 36 patients (33 men, 3 women; 39-82 yr old), 29 specimens from primary tumors and 7 from regional metastatic sites. Aneuploid states were recognizable in 30/36 specimens. The stages G1/0, S, and G2 + M were analyzed. The histograms of 26 aneuploid tumors revealed two peaks consisting of the G1/0 populations of tumor cell and the G1/0 peak due to normal diploid cells within the carcinomatous tissue. Four histograms showed only on G1/0 peak each, expressing an almost pure tumor cell population. One tumor specimen showed three aneuploid peaks indicating a multiclonal growth pattern. In six tumor specimens, the euploid pattern of nuclear DNA was confirmed. In 28 histograms, hyperdiploid cell stem lines were found and and in two others, hypoploidy. DNA index values ranged from 0.59 hypodiploid to 3.24 hyperhexaploid state, with a mean of 1.55. Considerable variability in cell cycle phase distribution was observed. The results indicated that the aneupioid deviation from the regular euploid state of the nuclear DNA represents a hallmark of nuclear abnormality in neoplastic tissues. (26 Refs)

17. DNA DETERMINATION IN THE CYTOLOGICAL DIAGNOSIS OF THYROID TUMORS WITH FOLLICULAR STRUCTURE.

Lukacs G, Balazs Gy, Zs-Nagy I, Csaky G, Fabrian E
I. Sebeszeti Klinika, Debreceni Orvostudomanyi Egyetem, Debrecen, Hungary
Magy Onkol; 26(2):197-205 1982

Cytofluorometric determination of the DNA content in cell nuclei and cytochemical tests were performed in fine-needle biopsy specimens obtained from 75 patients with suspected malignant thyroid tumors. Strongly increased DNA levels were found in the cell nuclei in undifferentiated thyroid tumors in agreement with the high proliferation rate of these tumors. The increase was smaller in medullary tumors. The investigation of the nuclear DNA levels in tumors with follicular structure revealed a shift from diploid toward tetraploid DNA levels, indicative of the presence of two different cell populations, in the patients with follicular adenomas. The DNA levels in follicular carcinomas were found to range from diploid to octoploid (2c-8c), with 10.3% of the cells being beyond 8c. These results show pronounced aneuploidy in follicular carcinoma. Examinations of the nuclear DNA levels in multiple nodules from the same patient revealed significantly higher DNA levels in follicular adenomatous components than in follicular or medullary carcinomatous components. The findings indicate the value of DNA cytofluorometry in the differential diagnosis of thyroid adenomas and carcinomas with follicular structures. (25 Refs) (In HUN)

18. NUCLEAR FEULGEN DNA CONTENT AND NUCLEAR SIZE IN HUMAN BREAST CARCINOMA.

Fossa SD, Marton PF, Knudsen OS, Kaalhus O, Bormer O, Vaage S
General Dept., Norsk Hydro's Inst. Cancer Res., Norwegian Radium Hosp., Oslo, Norway
Hum Pathol; 13(7):626-630 1982

Biopsy specimens from 29 patients with operable breast carcinomas were examined by Feulgen-DNA microspectrophotometry. A diploid DNA stemline was found in 10 tumors, 7 of which were Stage I carcinomas. In 19 tumors, 10 of which were Stage II cancers, a non-diploid DNA stemline was observed. The diploid tumors were most often estrogen receptor-positive (9 of 9 examined carcinomas), whereas 13 of 19 non-diploid carcinomas studied did not contain estrogen receptors. The mean nuclear size of the non-diploid tumor cells was increased compared with that of the diploid malignant cells. Three Grade I carcinomas were diploid, whereas three Grade III tumors were non-diploid. Of the 23 Grade II carcinomas, 7 were diploid and 16 non-diploid. (Author abstract) (22 Refs)

19. PLOIDY, PROLIFERATIVE ACTIVITY AND ESTROGEN RECEPTOR CONTENT IN HUMAN BREAST CANCER.

Raber MN, Bargolie B, Latreille J, Bedrossian C, Fritsche H, Blumenschein G
Oncology Div., Univ. Texas Medical Sch., 6431 Fannin St., Houston, TX, 77030
Cytometry; 3(1):36-41 1982

DNA flow cytometry was used in the analysis for ploidy and proliferative activity in 80 patients with breast cancer (43 primary, 37 metastatic). Estrogen receptor (ER) content was examined in 61 tumors (40 primary, 21 metastatic). Ploidy analysis showed that 68/80 tumors (65%) were hyperdiploid. A unimodal ploidy distribution was seen in 73 tumors; in 7 there were two distinct aneuploid subpopulations. The degree of ploidy abnormality was not related to extent of disease or menopausal status but was higher in poorly differentiated tumors. There was a higher proportion of diploid tumors in the ER-positive group (7/31 versus 3/30 ER-negative). DNA content was constant in biopsies from multiple sites in five patients with metastatic disease and in serial biopsies over the course of the disease. Proliferative activity, as indicated by percentage of cells in the S phase, was not related to extent of disease and menopausal status. High proliferative activity was more often associated with ER-negative tumors than ER-positive tumors, although there was a wide range of values in all subgroups. There was no significant increase in proliferative activity associated with increasing number of positive nodes at time of surgery or with increasing clinical stage. It is concluded that flow cytometric analysis of cellular DNA content provides a rapid means of quantitating ploidy and proliferative activity in human breast cancer. (40 Refs)

20. PROGNOSTIC FACTORS IN CHONDROSARCOMA. A COMPARATIVE STUDY OF CELLULAR DNA CONTENT AND CLINICOPATHOLOGIC FEATURES.

Kreicbergs A, Boquist L, Borssen B, Larsson SE
Dept. Orthopedic Surgery, Karolinska Hosp., S-104 01 Stockholm, Sweden
Cancer; 50(3):577-583 1982

In a retrospective study of 45 surgically treated chondrosarcomas, the prognostic significance of the cellular DNA content and different clinicopathologic factors was analyzed both separately and in combination. The relationship between these parameters was also investigated. Diploid (normal DNA content) chondrosarcomas were associated with a significantly (p less than 0.001) higher 10-yr survival rate than hyperploid (abnormally increased DNA content) chondrosarcomas. Apart from ploidy, factors such as tumor size, tumor location and tumor grade also proved to be of prognostic importance. However, patients with diploid tumors had a better prognosis than those with hyperploid tumors, almost regardless of location, size, grade or even treatment. Nevertheless, additional prognostic information could be obtained by combining ploidy with size, location and grade of the tumors. Ploidy and treatment were significantly related to the 10-yr recurrence rate. No statistical relationship could be demonstrated between ploidy and other prognostic factors. A strong correlation (p less than 0.001) was, however, found between location and size of the tumors. Thus, distal tumors were significantly smaller and, moreover associated with a better prognosis than axial tumors. The results indicate that ploidy probably is the best predictor of the clinical course in chondrosarcoma. While tumor location and size may be assumed to determine the conditions for radical surgery, ploidy and grade seem to reflect the inherent biological malignancy in chondrosarcoma. Consideration of all these factors seems to provide not only valuable prognostic information, but also guidelines for treatment. (Author abstract) (17 Refs)

21. DNA DISTRIBUTION IN HUMAN COLON CARCINOMAS AND ITS RELATIONSHIP TO CLINICAL BEHAVIOR.

Wolley RC, Schreiber K, Koss LG, Karas M, Sherman A
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JNCI; 69(1):15-22 1982

Striking differences in outcome of surgically treated colon adenocarcinomas were observed in 33 patients according to the DNA distribution patterns in tumor nuclei, measured by flow cytometry. As discussed and defined in the text and confirmed by appropriate control studies, the tumors were classified into two groups: predominantly diploid (20 tumors) and predominantly nondiploid (13 tumors). During the follow-up period of 3-5 yr. Twelve of the 13 patients with 'nondiploid' tumors died of disease within 4-34 mo, and the 1 patient still alive after 59 mo has extensive metastases. Only 6 of the 20 patients with 'diploid' tumors died of disease, sometimes after a slow, protracted clinical course. There were 14 patients with no evidence of disease for periods ranging from 30 to 60 mo; 1 of these patients died of other causes. Histologic grading and Dukes' staging appeared to play a relatively limited role in the outcome, although lymph node metastases and vascular invasion were more often observed in the nondiploid tumors. These observations suggest that the determination of DNA distribution in colon carcinomas may prove to be of prognostic value. (Author abstract) (40 Refs)

22. FLOW CYTOMETRIC ANALYSIS OF R3327 RAT PROSTATE ADENOCARCINOMA GROWN IN VIVO AND IN VITRO.

Claflin AJ, Pollack A, Malinin T, Block NL, Irvin GL
Dept. Surgery, Univ. Miami Sch. Medicine, P.O. Box 016960, Miami, FL, 33101
JNCI; 69(1):79-87 1982

The Dunning R3327 transplantable prostate adenocarcinoma in the Copenhagen rat is an acceptable model for the human disease. The G-subline (a rapidly growing carcinoma) and the H-subline (a slow-growing, well-differentiated adenocarcinoma) represent the extremes of differentiation and growth rate of this tumor. Both sublines were found to have one population that was diploid and a second aneuploid population that was hyperdiploid in DNA content. The percentage of hyperdiploid cells was significantly higher in R3327-G tumors than in R3327-H tumors. The tumor cell population ratios were stable in vivo, but the in vitro culture conditions supported only cells with diploid DNA content following four to five subcultures. These predominantly diploid cultured cells, when injected into intact male rats, resulted in tumors that had both diploid and aneuploid cells. (Author abstract) (14 Refs)

23. SIGNIFICANCE OF THE BARR BODY IN HUMAN FEMALE TUMORS.

Ghosh SN, Shah PN
Endocrinology Div., Cancer Res. Inst., Tata Memorial Centre, Bombay 400 012, India
Cancer Genet Cytogenet; 4(3):269-274 1981

The significance of the Barr body in human female tumors is reviewed with regard to the distribution of the Barr body in teratomas and other malignant tumors; Barr body frequency (BBF) and ploidy, prognosis, and hormone responsiveness in breast cancer; loss of the Barr body and its probable mechanism; and BBF and estrogen receptor status of breast cancer. (47 Refs)

CHROMOSOMAL FRAGILITY AND GENETIC FACTORS PREDISPOSING TO HUMAN CANCER

24. A FAMILIAL AGGREGATION OF PANCREATIC CANCER: AN IN VITRO STUDY (MEETING ABSTRACT).

Danes BS, Lynch HT
Cornell University Medical College, New York, NY
Proc Am Assoc Cancer Res; 23:152 1982

Solid clues for the epidemiology of pancreatic cancer have been exceedingly limited. Although familial aggregations of pancreatic cancer have been observed, genetic versus environmental roles have not been clarified. Biomarker research harbors the potential for identifying members at increased cancer risk due to their genotype within such aggregates. In vitro research has been based on the hypothesis that normal cells from a skin biopsy when grown in culture show in vitro expressions of cancer prone genes; one of these is alterations in chromosome complement number. This hypothesis was tested in studies of such a family. Diploidy has been a constant feature of such cultures derived from normals (without a family cancer history). Hyperdiploidy with the exception of tetraploidy has rarely been observed. Cultures established from 17 family members could be divided into two groups: 1) with and 2) without hyperdiploidy. Cultures from 9 family members, 7 family members by-marriage and 10 non-family members showed normal tetraploidy and no other hyperdiploidy. The other 8 family members had increased hyperdiploidy exclusive of normal tetraploidy. This was the first demonstration of an in vitro abnormality showing vertical transmission in 2 consecutive generations in a familial pancreatic cancer aggregate. An extension of such an in vitro approach to other such clusters may help to clarify factors in the etiology of pancreatic cancer. (no Refs)

25. FAMILIAL RESPIRATORY CARCINOMA: ECOGENETICS OF LUNG CANCER (MEETING ABSTRACT).

Goffman TE, Hassinger DD, Mulvihill JJ
Clinical Epidemiology Branch, National Cancer Institute, Bethesda, MD, 20205
Proc Am Soc Clin Oncol; 1:C-573 1982

Two families with excessive respiratory tract cancers underwent comprehensive evaluation including physical examination, routine laboratory studies, pulmonary function studies, sputum cytologic analysis, assay for quantitative immunoglobulins, tumor markers and lymphocyte karyotyping. In both families, the influences of smoking and, to a lesser extent, occupational exposures were evident risks. Both familes had members with multiple primary cancers and radiogenic tumors in young members, suggestive of inherent predisposition to environmentally induced neoplasia. Further, Family B had a newly recognized syndrome of limb and dental anomalies, and, independently, two members were carriers of a balanced translocation between chromosomes 13 and 14. Efforts were made to prevent further respiratory tract cancer deaths, to search for laboratory markers of risk, and to store blood and tissue specimens for assays in development. (no Refs)

26. ATAXIA-PANCYTOPENIA: SYNDROME OF CEREBELLAR ATAXIA, HYPOPLASTIC ANEMIA, MONOSOMY 7, AND ACUTE MYELOGENOUS LEUKEMIA.

Li FP, Hecht F, Kaiser-McCaw B, Baranko PV, Potter NU
Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Cancer Genet Cytogenet; 4(3):189-196 1981

In a family with ataxia and pancytopenia, the proband had cerebellar ataxia, developed hypoplastic anemia at age 3 yr, and died of acute myelomonocytic leukemia at age 7. Serial cytogenetic studies of the proband's hypoplastic bone marrow over a 25-mo period revealed progressive expansion of a clone of cells with C(6-12 + X) monosomy from 33% to 94% of metaphases. The missing chromosome by banding was deduced to be No 7. No increased sensitivity of the patient's cells was found in response to ultraviolet or ionizing radiation or to mitomycin C. Cerebellar atrophy was confirmed at autopsy. Family studies revealed cerebellar ataxia in the proband's father and all four siblings. Two brothers, including one with C-monosomy, died with hypoplastic anemia and another brother died with acute myelocytic leukemia. The only surviving sibling is a 19-yr-old sister who has unexplained anemia, decreased mitotic activity in bone marrow, and slow progressive cerebellar ataxia. The name ataxia-pancytopenia syndrome is proposed to encourage study of additional patients with this disorder, which predisposes to pancytopenia and acute leukemia. (Author abstract) (25 Refs)

27. NEPHROBLASTOMA AND THE 11P CHROMOSOME (MEETING ABSTRACT).

Ellis PM, Grace E, Bauld R, Bain AD
University Department of Pathology, Royal Hospital for Sick Children, Edinburgh, Scotland
J Med Genet; 19(1):63 1982

The association between nephroblastoma, eye defects, mental retardation, and a specific chromosome abnormality has previously been reported. Our experience with this association, although necessarily limited, poses many questions relevant to diagnosis, prognosis, and treatment in affected children. Scant attention appears to have been paid to the possibility of specific histological features in these tumors. The relationship of such features to persistent renal blastema is of considerable interest. In infants and children referred for chromosome analysis because of psychomotor retardation or odd facial features and found to have an 11p deletion, continued clinical surveillance throughout childhood would appear mandatory, bearing in mind the possibility of subsequent development of nephroblastoma. Such monitoring could include regular ultrascan. Until more information concerning the association emerges it would be of value to karyotype blood of all children with nephroblastoma, as well as the tumor itself. Finally, the prognosis for children with this particular association between tumor and chromosome abnormality remains open to debate. (no Refs)

28. CHROMOSOMAL ABNORMALITIES IN RETINOBLASTOMA CELLS.

Kuznetsova LE, Prigozhina EL, Pogosiants EE, Belkina BM, Kuzina NK
Center for Oncology Res., USSR Acad. Medical Sciences, Moscow, USSR
Vopr Onkol; 28(5):67-70 1982

The karyotype of seven unilateral retinoblastomas was studied. Loss or a gain of chromosomes and structural chromosomal changes were observed in all tumors. Modal chromosome number was pseudodiploid in four and near-diploid in three tumors. There were no sex chromosomes (X or Y) in three tumors. Four tumors were characterized by the presence of an identical marker chromosome - i(6p). Two other markers -1p+ and 17q+ (probably, not quite identical) - were present in four and three tumors, respectively. The cells of two retinoblastomas contained both i (6p) and 17q+ markers. (Author abstract) (10 Refs) (In RUS)

CHROMOSOMES OF HUMAN CELL LINES AND TUMORS IN VITRO

29. CHROMOSOMES OF HUMAN HEPATOMA CELL LINES.

Simon D, Aden DP, Knowles BB
Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA, 19104
Int J Cancer; 30(1):27-33 1982

The karyotypes of three human hepatoma cell lines Hep G2, Hep 3B and PLC/PRF/5 were investigated by G-and C-banding techniques. In addition to ploidy changes, typical for most carcinoma cell lines, certain markers were found that remained stable throughout passage of these cultures. Chromosome 1 is involved in multiple translocations, resulting in at least three copies of the chromosome 1 heterochromatin region in each cell line. Inversion in the 9qh region is also seen. In addition, each of the cell lines consistently contains trisomy of 17q. The rearrangements of chromosome 1 are more striking in the Hep 3B and PLC/PRF/5 cell lines, which are derived from human hepatocellular carcinomas and contain integrated copies of the hepatitis B viral genome. These two cell lines are characterized by the presence of at least five copies of the 1 (p13 to q21) region that result from multiple deletions and/or translocations; by consistent trisomy and polymorphism of the 9qh region; and by trisomy of chromosome 10 (also involved in rearrangements). The Hep G2 and Hep 3B cell lines behave functionally as highly differentiated liver parenchymal cells and are karyologically distinguishable from PLC/PRF/5 both by the presence of trisomy of 6 (pter to q14) and by the finding that one of the homologues of chromosome 15 is 15q+. (Author abstract) (29 Refs)

30. CHROMOSOME ABNORMALITIES IN JAPANESE BURKITT LYMPHOMA CELL LINES.

Hamasaki K

Second Dept. Internal Medicine, Okayama Univ. Medical Sch., Okayama 700, Japan

Acta Med Okayama; 36(1):23-38 1982

Six established Japanese Burkitt lymphoma (BL) cell lines including one case with null cell type were studied by chromosomal banding techniques. The modal chromosome number was diploid or nearly diploid in five cases and hyperdiploid in one case. The marker chromosome 14q+ was observed in four of the six cases; the origin of the extra band was a chromosome 8 in three including the null cell case but could not be identified in the other. The two cases lacking the 14q+ marker had variant translocations involving the long arm of chromosome 8, one of which carried a translocation, t(8;22) (q24;q13) and the other a translocation, t(2;8) (p12;q24). Although structural and/or numerical aberrations were found in all six cell lines, chromosome 8 was the one most consistently involved. This frequent involvement of chromosome 8 in aberrations, therefore, may be an important event in the development of BL rather than the presence of a 14q+ marker chromosome. (Author abstract) (44 Refs)

31. STRUCTURAL AND NUMERICAL CHROMOSOME ABNORMALITIES IN HUMAN MALIGNANT MELANOMA CELL LINES.

Bertrand S, Leftheriotis E, Dore JF

Centre Leon-Berard, 28, rue Laennec, 69373e Lyon, France

C R Seances Acad Sci [III]; 294(11):459-462 1982

Biopsies from 29 patients with malignant melanomas (2 primary tumors, 7 metastatic adenopathies, 5 local recurrences, 11 ganglionic recurrences, 2 distant cutaneous metastases, and 2 pleural washings) yielded 36 cell lines which most frequently demonstrated structural abnormalities of chromosomes 1, 2, 3, 6, 7, 9, 11, 12, and 22. Partial or total disappearance of chromosomes was observed most frequently in 8, 9, 13, and 18. Multiple copies were observed for chromosomes 3, 7, 16, 19, 20, and 22. Structural abnormalities of chromosome 7 occurred in all metastatic cell lines, and multiple copies of chromosome 7 were observed in cell lines from primary or recurrent tumors. (20 Refs) (In FRE)

CHROMOSOMES OF ANIMAL CELL LINES AND TUMORS

32. EVIDENCE FOR THE CLONAL ORIGIN OF SPONTANEOUS METASTASES.

Talmadge JE, Wolman SR, Fidler IJ
(c/o Fidler) Cancer Metastasis and Treatment Lab., NCI, Frederick Cancer Res. Facility, Frederick, MD, 21701

Science; 217(4557):361-363 1982

A cultured cell line of the K-1735 melanoma was x-irradiated to induce chromosome breakage and rearrangements and then was implanted into the footpads of syngeneic C3H mice. Spontaneous lung metastases were isolated from different animals, established in culture as individual lines, and then karyotyped. Within certain metastases, the same chromosomal abnormality (or abnormalities) (recombinant chromosomes) was found in all the cells examined. Most metastases differed from one another in that they exhibited characteristic combinations of chromosomal markers. These findings indicated that the metastases were clonal and that they probably originated from different progenitor cells. (Author abstract) (45 Refs)

33. TUMOR INVASION: TUMOR-HOST CELL INTERACTION AND COLLAGENASE PRODUCTION (MEETING ABSTRACT).

Dabbous MK, Luthardt F, Haney L, El-Torky M, Brinkley B
Department of Biochemistry, University of Tennessee Center for Health Science, Memphis, TN, 38163

Proc Am Assoc Cancer Res; 23:36 1982

The potential role of collagenolytic enzymes in tumor invasion has been previously suggested. However, the question whether or not the invading tumor cells are capable of producing collagenase remained unclear. Primary cultures of rabbit VX-2 carcinoma produced high levels of collagenase activity in both active and latent forms in serum free media. Two morphologically distinct cell types; epithelial-like (E-cells) and fibroblast-like (F-cells) were separated from these cultures. In early passages, both cell types were tumorigenic producing tumors which were histologically similar to the original tumor from which the cells were derived. The presence of tonofibrils and desmosomal junctions suggested the epithelial origin of the tumor cells. Collagenase production by F-cells increased as a function of passage number for six passages then sharply fell to a normal low level while in the E-cells the level of enzyme activity remained approximately constant for additional few passages. Cytogenetic studies demonstrated that the E-cells were characterized by numerical and structural chromosomal changes which remained constant subsequent to serial in vitro culture and in vivo transplants. Analysis of G-banded chromosomes from E-cells revealed a modal number of 54 with relatively few normal chromosomes and a variety of distinctive, unidentifiable marker chromosomes. Except for a small percent, the F-cells contained normal diploid complement with sex chromosomes corresponding to that of the host. The E-cells appeared to be of tumor origin whereas the F-cells are mainly of host origin. (no Refs)

34. INHERITANCE OF CELLULAR RESISTANCE TO THE ANTITUMOR AGENT ICRF 159 IN SOMATIC CELL HYBRIDS.

Edgar DH, Creighton AM
(c/o Creighton) Cellular Pharmacology and Antitumour Chemistry Lab., Imperial Cancer Res. Fund,, Lincoln's Inn Fields, London WC2A 3PX, England

JNCI; 68(6):977-980 1982

Two independently derived sublines of Syrian hamster BHK 21S cells that demonstrate resistance to the antitumor agent ICRF 159 (NSC-129943) were fused to sensitive cells in both intraspecific and interspecific crosses, and the responses of the resultant hybrids to the drug were determined. In intraspecific hybrids from crosses involving either of the sublines, resistance to ICRF 159 was expressed codominantly with hybrid response being halfway between the parental responses. In interspecific hybrids from crosses with sensitive mouse cells, resistance was also expressed but to a lesser extent than in the intraspecific hybrids. However, subsequent passaging of an interspecific hybrid resulted in an increase in the degree of resistance, which appeared to be accompanied by a loss of telocentric mouse chromosomes. The results suggested that resistance in these lines was due to an alteration in the cellular target involved in the response to ICRF 159. (Author abstract) (21 Refs)

GENE MAPPING STUDIES

35. CHARACTERIZATION OF TUMORIGENIC PROTEINS.

Stitt DT
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Diss Abstr Int [B]; 42(6):2348-B 1982

The 17K, 84K, and 94K SV40 T antigens from SV40 permissive and transformed cells were analyzed by tryptic peptide mapping on ion exchange columns. The 48K and 55K nonviral antigens, proteins immunoprecipitable by SV40 T antibody from SV40 permissive and transformed cells, were compared to the SV40 large T antigen and to each other by tryptic peptide mapping. The 48K and 55K nonviral antigens are not degradation products of the SV40 T antigens and at most are only slightly related to the SV40 T antigens. The 48K and 55K nonviral antigens are slightly related to each other, sharing about 3 methionine containing tryptic peptides. Four SV40 transformed human cell lines, one SV40 transformed mouse cell line, and eight SV40 transformed human/mouse somatic cell hybrid cell lines were examined for the expression of nonviral antigens. Differences were found in the patterns of expression of the nonviral antigens among the human cell lines, between the human and the mouse cell lines, and between the human/mouse somatic cell hybrid cell lines and the human lines from which they were derived. By comparing the tryptic peptides fractionated on cation exchange columns of the nonviral antigens it was determined that: (1) The 48K nonviral antigen in human/mouse hybrids is encoded by a mouse chromosome. (2) The 52K nonviral antigen in the Balb IV-8 human/mouse hybrid is encoded by a mouse chromosome and is probably a precursor to the mouse 48K nonviral antigen. (3) The 55K nonviral antigen in the C57-VII-6 human/mouse hybird is encoded by a human chromosome; while in the Balb IV-8 human/mouse hybrid the 55K protein band is encoded by a human chromosome and probably by a mouse chromosome also. (4) If the gene encoding the human nonviral antigen is located on a single chromosome, it is located on human chromosome 7. (no Refs)

MOLECULAR CYTOGENETICS

36. HUMAN DNA SEQUENCE HOMOLOGOUS TO THE TRANSFORMING GENE (MOS) OF MOLONEY MURINE SARCOMA VIRUS.

Watson R, Oskarsson M, Vande Woude GF
Lab. Molecular Oncology, NCI, NIH, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 79(13):4078-4082 1982

We describe the molecular cloning of a 9-kilobase-pair BamHI fragment from human placental DNA containing a sequence homologous to the transforming gene (v-mos) of Moloney murine sarcoma virus. The DNA sequence of the homologous region of human DNA (termed humos) was resolved and compared to that of the mouse cellular homolog of v-mos (termed mumos). The humos gene contained an open reading frame of 346 codons that was aligned with the equivalent mumos DNA sequence by the introduction of two gaps of 15 and 3 bases into the mumos DNA and a single gap of 9 bases into the humos DNA. The aligned coding sequences were 77% homologous and terminated at equivalent opal codons. The humos open reading frame initiated at an ATG found internally in the mumos coding sequence. The polypeptides predicted from the DNA sequence to be encoded by humos and mumos also were found to be extensively homologous, and 253 of 337 amino acids were shared between the two polypeptides. The first five NH2-terminal and last two COOH-terminal amino acids of the humos gene product were in common with those of mumos. In addition, near the middle of the polypeptide chains, four regions ranging from 19 to 26 consecutive amino acids were conserved. However, we have not been able to transform mouse cells with transfected humos DNA fragments or with hybrid DNA recombinants containing humos and retroviral long terminal repeat (LTR) sequences. (Author abstract) (28 Refs)

37. CELL CYCLE REGULATION OF DNA REPAIR (MEETING ABSTRACT).

Gupta PK, Sirover MA
Fels Research Institute, Temple University School of Medicine, 3420 North Broad Street, Philadelphia, PA, 19140
Med Pediatr Oncol; 10(1):101 1982

The capacity of human cells to modulate DNA repair pathways were examined. Synchronous cultures of WI-38 normal diploid fibroblasts were used to investigate whether DNA repair pathways were modulated during the cell cycle. Two criteria were used: 1) unscheduled DNA synthesis (UDS) in the presence of hydroxyurea after exposure to ultraviolet light; to N-acetoxy-acetylaminofluorene (N-AcO-AAF); to methyl methanesulfonate (MMS); or to sodium bisulfite; and 2) repair replication into parental DNA in the absence of hydroxyurea. DNA repair measured as UDS after UV irradiation or after exposure to N-AcO-AAF was induced 2-3 fold in WI-38 fibroblasts during the cell cycle reaching a maximum in cultures exposed 14-15 hrs after stimulation. Base excision repair measured after exposure to MMS or sodium bisulfite was similarly stimulated and reached a maximum at an interval of 18 hrs in the cell cycle. Similar results were observed using repair replication into parental DNA in the absence of hydroxyurea. In either instance DNA repair was sequentially stimulated prior to the induction of DNA replication which was maximal at an interval of 22-24 hrs of the cell cycle. These results suggest that normal human cells stimulate DNA repair pathways prior to DNA replication to remove DNA lesions before DNA is copied. This would ensure the transfer of correct genetic information to daughter cells and may provide a mechanism by which human cells seek to reduce mutagenesis or carcinogenesis after exposure to environmental agents. (no Refs)

38. EFFECT OF FORMALDEHYDE ON DNA DAMAGE AND REPAIR IN HUMAN BRONCHIAL EPITHELIAL CELLS AND FIBROBLASTS (MEETING ABSTRACT).

Grafstrom RC, Fornace AJ, Harris CC
Laboratory of Human Carcinogenesis, National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:266 1982

The alkaline elution technique was used to study damage and repair of DNA in human bronchial epithelial cells (BE) and fibroblasts (BF), skin fibroblasts (SF) and XP12BE xeroderma pigmentosum (XP) skin fibroblasts. Exposure of cells to formaldehyde (HCHO) resulted in the formation of DNA-protein crosslinks (DPC) and DNA single strand breaks (SSB). All cell types showed a similar dose-response to HCHO with regard to the formation and disappearance of DPC. After exposure of the cells to doses between 0.1 ad 2.0 mM HCHO for 1 hr, the crosslinks were removed with a half-removal time of 2 to 3 hr. After 10 hr of post-treatment incubation, less than 10% of the DPC remained. In the presence of the repair polymerase inhibitors, 1-beta-D-arabinofuranosylcytosine and hydroxyurea, approximately 1 DNA SSB per 10(9) daltons accumulated in BF, BE, and SF cells in 4 hrs after treatment of the cells with 0.8 mM HCHO for 1 hr. In contrast, no SSB accumulated in XP cells with the same regimen of HCHO and polymerase inhibitors. These results indicate that HCHO induces DNA damage that is repaired by the UV-type excision repair pathway. A dose of 0.1 mM HCHO induce no detectable SSB in BE and BF. However, the same concentration of HCHO significantly inhibited the repair of x-ray-induced DNA SSB. A 5 to 10-fold higher concentration was required to inhibit unscheduled DNA synthesis induced by UV radiation or anti-benzo(a)pyrene diolepoxide. (no Refs)

39. REPAIR OF DNA-PROTEIN CROSSLINKS DURING INHIBITION OF PROTEIN AND DNA SYNTHESIS IN NORMAL HUMAN FIBROBLASTS (MEETING ABSTRACT).

Taylor WG, Gantt R, Camalier F, Stephens EV
National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:265 1982

X-rays, ultraviolet light, visible fluorescent light, and various chemicals can induce DNA-protein crosslinks in mammalian cells in culture. Though these lesions are a small proportion of the total damage inflicted on the genome, crosslinks have been implicated in transformation of 3T3 and 10T1/2 cells, induce sister chromatid exchanges, and may be important in carcinogenesis. DNA-protein crosslinks induced by trans-diaminodichloro-platinum (II) were assayed at appropriate times by the membrane alkaline elution procedure of Kohn. Results show that human fibroblasts repair DNA-protein crosslinks while S-phase DNA synthesis is completely inhibited by aphidicolin (10 ug/ml). This clearly shows DNA synthesis is not coupled to the repair of these lesions. When protein synthesis is inhibited with cycloheximide (5 ug/ml), repair of the trans-Pt induced

DNA-protein crosslinks is delayed: approx 50% are repaired in 24 hr with little thereafter. Neither the time nor the extent of this partial repair of crosslinks is affected when cells are preincubated for 17 hr with cycloheximide before trans-Pt treatment. These results indicate that the partial repair is not due to turnover in the absence of re-synthesis of required proteins. The repair could result from 'leaky' cycloheximide-insensitive (up to 10 ug/ml) synthesis of a required protein(s) or from the presence of two classes of crosslinks, one of which requires protein synthesis for repair. (3 Refs)

40. HSRS AND DMS IN CELLS WITH ACQUIRED RESISTANCE TO VINCRISTINE (MEETING ABSTRACT).

Biedler JL, Meyers MB, Spengler BA
Sloan-Kettering Institute for Cancer Research, Rye, NY
Am J Hum Gen; 33(6):5A 1982

It is now well established that the HSRs (homogeneously staining regions) of metaphase chromosomes and DMs (double minutes) can be the sites of amplified DNA sequences encoding dihydrofolate reductase. Most human neuroblastoma cells in culture, although under no obvious selection pressure, such as drug exposure, also exhibit either HSRs or DMs. This observation and additional lines of evidence suggest that the chromosomal anomalies are alternative cytological manifestations of the same phenomenon. Vincristine-resistant cells constitute a newly developed system with similar cytological attributes. Chinese hamster lung cells, DC-3F/VCRd-5, selected by stepwise increase in concentration of vincristine are characterized by an HSR on an abnormal, marker chromosome (9+HSR+Xq). Revertant VCRd-5-U cells maintained in vincristine-free medium showed a decline in resistance and HSR length. Two-dimension (D) gel electrophoresis demonstrated increased synthesis of a 19 KD acidic (pI equals 5.7) protein, designated V19, in the resistant cells. Further, in vitro translation of poly(A) RNA from sensitive, resistant, and revertant cells and 2D gel analysis of the translation products showed a markedly increased synthesis of V19 in DC-3F/VCRd-5 cells, suggesting an increased amount of V19-specific mRNA. Vincristine-resistant human neuroblastoma cells likewise display chromosomal abnormalities as compared to controls. SH-SY5Y/VCR cells are characterized by the presence of 10-100 DMs. The MC-IXC/VCR neurblastoma clone was selected from the parental SK-N-MC line which had a short HSR on a 22q in about 20% of the cells. The vincristine-resistant cells typically contain a new HSR on a 19p. Both drug-resistant human neuroblastoma lines oversynthesize a 26 KD protein, pI 5.7. The HSRs and DMs of the various vincristine-resistant cells appear to represent another example of DNA sequence amplification in response to drug challenge. (no Refs)

41. HSRS AND DMS IN TWO TUMORS OF CHILDHOOD (MEETING ABSTRACT).

Balaban G, Gilbert F, Bahr G
University of Pennsylvania School of Medicine, Philadelphia, PA
Am J Hum Gen; 33(6):6A 1982

HSRs (homogeneously staining regions) and DMs (double minutes) have been identified in a series of human neuroblastomas (both in direct preparations from tumors and in cell lines in culture) and in one human retinoblastoma cell line. The HSRs are on different chromosomes (numbers 1, 5, 6, 7 and 13) in different lines. We have previously proposed that DMs can arise from the breakdown of an HSR. Cytogenetic studies of the HSR/DMs will be described, as will an analysis of gene amplification in cell lines containing one or both of these abnormalities. (no Refs)

42. BOVINE PAPILLOMAVIRUS VECTOR THAT PROPAGATES AS A PLASMID IN BOTH MOUSE AND BACTERIAL CELLS.

DiMaio D, Treisman R, Maniatis T

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Proc Natl Acad Sci USA; 79(13):4030-4034 1982

We report the construction of a bovine papillomavirus (BPV)-derived recombinant plasmid that propagates as an extrachromosomal element in both mouse and bacterial cells. Plasmids composed of a subgenomic transforming fragment of BPV DNA, a deletion derivative of pBR322, and a 7.6-kilobase fragment of DNA from the human beta-globin gene cluster efficiently induce focus formation on mouse C127 cells. PBV-beta-globin hybrids are maintained in the transformed cells as plasmids with a copy number of about 10-30 per cell. Plasmids indistinguishable from the input DNA have been recovered by transformation of bacteria with low mol wt DNA from transformed mouse cells. The human beta-globin gene linked to BPV DNA is transcribed from its own promoter at a high level in these cells. The expression of BPV-linked cellular genes in conjunction with the ability to shuttle DNA between bacteria and mammalian cells may provide a rapid means of analyzing and recovering genes that confer an identifiable phenotype upon mammalian cells. (Author abstract) (31 Refs)

43. DIVERSE XENOTROPIC VIRUS EXPRESSIONS IN TWO NZB MOUSE BREEDING LINES THAT DIFFER IN CHROMOSOME BREAKAGE.

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JNCI; 68(6):951-955 1982

Two breeding lines of the NZB/Bl mouse strain, which was originated from Bielschowsky's stock and maintained as a conventional inbred colony since 1963, were developed by selective matings according to chromosome breakage incidence in bone marrow cells. These breeding lines were used because they represent an interesting experimental model, since they differ in the manifestations of the autoimmune process and the incidence of lymphomas. The present study showed that embryos from both breeding lines differed in the expression of the xenotropic type C RNA virus, characteristic of NZB mice. All 17 cultures initiated with embryos from the line showing high chromosome breakage (HB) had positive reverse transcriptase (RT) reactions after cocultivation with an indicator cell line (SIRC). On the contrary, only 3 of the 22 embryos from the line showing low chromosome breakage (LB) had RT activity at late passages (7-10). The chromosome studies done on these embryo cultures showed highly significant differences in the chromosome breakage incidence for the 2 breeding lines [10.6 and 20.5% of cells with aberrations for LB and HB embryos, respectively (P less than 0.001)] (Author abstract) (22 Refs)

44. TRANSFECTION WITH THE ISOLATED HERPES SIMPLEX VIRUS THYMIDINE KINASE GENES. II. EVIDENCE FOR AMPLIFICATION OF VIRAL AND ADJACENT CELLULAR DNA SEQUENCES.

Reyes GR, McLane MW, Hayward GS
Dept. Pharmacology and Experimental Therapeutics, Johns Hopkins Univ. Sch. Medicine, 725 North Wolfe St., Baltimore, MD, 21205
J Gen Virol; 60(part2):209-224 1982

We have previously described several series of biochemical transformation experiments in which small defined portions of herpes simplex virus (HSV-1 and HSV-2) DNA encompassing the thymidine kinase (TK) gene were introduced into Ltk- cells by the calcium transfection procedure. The presence of authentic virus TK enzyme in several subcloned cell lines derived from these experiments was confirmed by either the specific incorporation of [125I]iododeoxycytidine into their nuclei or the inhibition of cell growth by the antiviral drug arabinosyl thymine. A panel of 24 independent Ltk+ cell lines receiving either isolated virus DNA fragments or cleaved plasmid DNAs was examined by blot hybridization for both the presence and copy number of virus TK DNA sequences. Most cell lines contained a single virus DNA fragment covalently joined to host (or carrier Ltk(-)) mouse DNA sequences, but several contained multiple copies of the TK gene. Examination of the structural arrangement of the virus DNA in two early passage multicopy cell lines indicated that the TK gene had integrated into Ltk- cell DNA and then subsequently both viral and flanking cellular sequences were amplified to create up to 20 tandem duplications. In one case, mapping of the adjacent cellular sequences has revealed that the total repeat unit is greater than 23 kilobases (kb) in size. On subsequent passaging, even in HAT medium, the amplified repeat units were not stable and fell to only three to four copies per haploid cell genome. These cell lines should prove useful for additional studies to examine the expression of co-selected non-TK virus sequences and the influence of adjacent cellular DNA sequences on transcription and retransfection of the resident TK gene. (Author abstract) (45 Refs)

45. NON-IMMUNOGLOBULIN-ASSOCIATED DNA REARRANGEMENTS IN MOUSE PLASMACYTOMAS.

Harris LJ, Lang RB, Marcu KB
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Proc Natl Acad Sci USA; 79(13):4175-4179 1982

We have characterized a class of DNA rearrangements in plasmacytomas. These recombination events involve a DNA sequence whose origin is outside of the locus of the heavy chain constant region genes, CH. Therefore, we choose to refer to this sequence as non-immunoglobulin-associated rearranging DNA (NIARD). We have isolated two abortively rearranged C alpha genes, generated by NIARD events from the alpha-producing J558 myeloma. Restriction endonuclease maps of these sequences reveal two possible recombination sites in NIARD that are separated by approx 6.5 kilobase pairs of DNA (defined at 5' and 3' sites). A NIARD rearrangement occurs in 15 out of 20 plasmacytomas tested, including gamma3-, gamma1, gamma2b-, gamma2a-, and alpha-producers, but this event usually does not involve a CH switch (S) region. In fact, only S alpha appears to accept NIARD. However, NIARD did not undergo a rearrangement in eight IgA-producing hybridomas tested. One germ-line copy of NIARD (a 22-kilobase pair EcoRI fragment) is retained in all plasmacytomas. NIARD does not appear to possess repetitive DNA sequences homologous to S mu or S alpha. We discuss the possible role and implications of NIARD-like sequence rearrangements in allelic exclusion and chromosomal translocation events in plasmacytomas. (Author abstract) (30 Refs)

46. NOVEL CLASS OF MOUSE MAMMARY TUMOR VIRUS-RELATED DNA SEQUENCES FOUND IN ALL SPECIES OF MUS, INCLUDING MICE LACKING THE VIRUS PROVIRAL GENOME.

Callahan R, Drohan W, Gallahan D, D'Hoostelaere L, Potter M

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Proc Natl Acad Sci USA; 79(13):4113-4117 1982

Mice in breeding colonies of feral Mus musculus brevirostris (Azrou, Morocco), M m musculus (Studenec, Czechoslovakia), and M m molossinus (Fukuoka, Japan) were found to lack the mouse mammary tumor virus (MMTV-alpha) proviral genome in their germ line. MMTV-alpha proviral genomes have been found in all inbred strains of M musculus by using high-stringency nucleic acid hybridization conditions. We conclude that feral mice in these colonies are heterozygous for a limited number of MMTV-alpha proviral genomes and that those lacking them arose as a result of random chromosomal segregation. All mice in another breeding colony of feral M m musculus (Sladeckovce, Czechoslovakia) lack MMTV proviral genes. By relaxing the conditions of nucleic acid hybridization, MMTV-related sequences (designted MMTV-beta) were detected in restricted cellular DNA from MMTV-negative mice and all other inbred strains and feral species of the genus Mus. The apparent ubiquity of the MMTV-beta DNA sequences in the genus Mus and the lack of variation in the pattern of restriction fragments containing these sequences within a species distinguishes from from MMTV-alpha. These results suggest that the MMTV-beta DNA sequences either are the evolutionary progenitors of the infectious MMTV genome or represent an accumulation of evolutionarily divergent MMTV-alpha insertions into the mouse germ line. (Author abstract) (35 Refs)

47. THE CHARACTERIZATION OF NON-HISTONE PROTEINS WHOSE AMOUNTS INCREASE IN CHROMATIN FROM MOUSE HEPATOCARCINOMAS.

Medvedev ZA, Buchanan JH, Medvedeva MN, Crowne HM

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Int J Cancer; 30(1):87-92 1982

A fraction containing liver- and hepatoma-specific non-histone proteins has been isolated from the chromatin of mice. Amino acid analysis of this fraction shows that it contains 16 mol of glutamic acid, 10 mol aspartic acid, 7 mol of both arginine and lysine per 100 mol and contains no cysteine or tyrosine. The proteins in this fraction are strongly associated with DNA and are co-extracted with histones from chromatin with 0.25 M HCl. In chromatin from age-related hepatomas, the amount of this fraction increased six-fold. This increase in concentration of these chromatin proteins may be associated with changes of chromatin structure necessary to initiate malignant growth in liver cells. (Author abstract) (33 Refs)

48. MOUSE MAMMARY TUMOR VIRUS GENE EXPRESSION: REGULATION VIA CHROMATIN STRUCTURE AND GLUCOCORTICOID HORMONES.

Feinstein SC
University of California, San Francisco, CA
Diss Abstr Int [B]; 42(10):4044-B 1982

Two mammary tumor virus (MTV) proviruses, integrated at different chromosomal loci in the genome of two clonal isolates of cultured rat hepatoma (HTC) cells, were investigated. One cell line, J2.17, epxresses MTV RNA only in the presence of glucocorticoid hormones, whereas proviral genes in the other line, J2.15, are not transcribed in the presence or absence of glucocorticoids; nonetheless, proviral genes and cellular components that mediate hormone responses appear intact and normal. Mild DNase I digestion of chromosomes in isolated nuclei reveals that the J2.17 MTV DNA sequences are packaged in highly DNase I sensitive chromatin, whereas J2.15 MTV chromatin is relatively nuclease resistant. These results demonstrate that the same genetic element, located at two different chromosomal loci within a single cell, can differ in both chromatin structure and gene expression. Analysis of the chromatin structure of appropriate DNA sequences in uninfected HTC cells suggests that the differences in the chromatin structure of the two proviruses reflects a 'spreading effect', in which integrating DNA is packaged into chromatin similar in configuration to surrounding chromatin. Thus, it is proposed that chromosomal position determines the folding pattern of newly introduced DNA sequences; this pattern in turn determines whether the genes can subsequently transcribe in response to the hormonal inducing signal. (no Refs)

49. MURINE ERYTHROLEUKEMIA CELL DIFFERENTIATION: DNASE I HYPERSENSITIVITY AND DNA METHYLATION NEAR THE GLOBIN GENES (MEETING ABSTRACT).

Sheffery M, Rifkind RA, Marks PA
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Proc Am Assoc Cancer Res; 23:138 1982

The sensitivity to digestion by DNase I of chromatin containing the alpha and betamaj globin genes and the pattern of DNA methylation near these genes was examined during hexamethylene bisacetamide (HMBA)-mediated erythroid differentiation of murine erythroleukemia cells (MELC). In uninduced and induced cells, the chromatin containing the alpha and betamaj globin genes are more sensitive to digestion by DNase I than the region containing an immunoglobulin gene (Igalpha) not expressed during erythroid differentiation. However, at low concentrations of DNase I, a 6 to 10-fold increase in site-specific cleavages were generated in chromatin regions near both the alpha and betamaj globin genes in cells induced to differentiate by HMBA. The DNase I hypersensitive site near the betamaj globin gene maps to a small region near the 5' terminus of the gene. No detectable change in the pattern of DNA methylation around either the alpha or beta globin genes was observed during HBMA-mediated erythroid differentiation. Of the potentially methylated sites assayed and mapped near the betamaj globin gene, one site is fully methylated, one is partially methylated, and one is unmethylated both in uninduced and induced cells. Many, but not all sites assayed near the alpha globin genes are unmethylated, both in uninduced and induced cells. These results show that specific alterations of chromatin structure occur during MELC differentiation and suggest that these changes may not involve alterations in the pattern of DNA methylation. (no Refs)

50. DNASE-I SENSITIVE DOMAINS WITHIN CHROMATIN OF HUMAN INTACT NEOPLASTIC CELLS (MEETING ABSTRACT).

Frenster JH, Masek MA, Frenster DA
Department of Medicine, Stanford University, Stanford, CA, 94305
Proc Am Assoc Cancer Res; 23:136 1982

Gene sequences actively transcribed to RNA within chromatin are characterized by the presence of DNA helix openings and by a selective sensitivity to digestion with DNase-I. Chromatin coiling and super-coiling may result in domains of such DNase-I sensitivity. Lymph nodes positive for the nodular sclerosis type of Hodgkin's Disease were fixed in the operating room after biopsy during pathologic staging of newly-diagnosed patients, and were then probed with acridine orange, digested with DNase-I, and examined by high-resolution transmission electron microscopy. Neoplastic Hodgkin's cells and Reed-Sternberg cells were identified by ultrastructural criteria, revealing discrete electron-dense reaction products confined to the transcription-active extended euchromatin portion of the cell nucleus. Omission of DNase-I resulted in complete absence of reaction products. The DNase-I sensitive domains range in size from 25-700 nm, equivalent to a minimum of 70-2000 base pairs in DNA helix length. DNase-I sensitive domains are found in increased numbers with those neoplastic cells which are early in their cell-differentiation sequence, and are reduced or absent within the most mature neoplastic cells in the cell-differentiation sequence. This distribution corresponds to the distribution of active DNA templates within these same cells. Domains of DNase-I sensitivity can thus be identified, measured, and counted within the intact chromatin of human neoplastic cells without disruption of these cells. (3 Refs)

51. STRUCTURAL AND FUNCTIONAL STUDIES OF THE TRANSFORMING PROTEIN OF RECOVERED AVIAN SARCOMA VIRUSES.

Karess RE
The Rockefeller University, New York, NY
Diss Abstr Int [B]; 42(9):3543-B 1982

The transforming protein, p60src, of recovered avian sarcoma viruses (rASV) was examined in detail, and compared with the p60src from nondefective Schmidt-Ruppin Rous sarcoma virus (SR-RSV) and with the p60-src homologue of normal cells. The enzymatic properties of the proteins obtained from these three sources were compared, and were shown to have very similar protein kinase activities. Proteolytic analysis with Staphylococcus aureus V8 protease, and trypsin were used to demonstrate an overall structural homology between rASV p60src and SR-RSV p60src. Methionine- and phosphate-containing peptides were generally indistinguishable between rASV and SR-RSV. However, a few leucine-containing peptides were consistently found in each of 14 rASV isolates, and were absent from the map of SR-RSV p60src. These rASV-specific peptides could be detected in the map of endogenous p60c-src. Such unique peptides serve as genetic markers, and demonstrate that the new src gene of rASVs is derived from the cellular c-src gene by genetic recombination. Large fragments of p60src, generated by various proteolytic activities, were also analyzed by tryptic digestion. This permitted the partial ordering of the peptides within the intact protein. Certain structural polymorphisms were found among the rASV p60srcs. In each case the variation was confined to the amino terminal portion of the protein. In two cases it appeared that slightly more c-src information was acquired at the amino terminus than was true for the majority of rASV isolates examined. One of these had apparently also suffered a small deletion near the N-terminus, resulting in a net shortening of the protein of 56,000 daltons. Despite the structural variations in p60src, all rASVs could transform cells in culture and induce tumors at the site of injection. However, the 56k variant consistently produced only tiny growths which eventually regressed. Possible explanations for the observed heterogeneity of the amino terminal structure are discussed. In light of the common origin and structure or rASV p60src and cellular p60c-src it is proposed that only the relative abundance of the former (under viral transcriptional control), is the cause of neoplastic transformation in infected cells. (no Refs)

52. A NOVEL SINGLE-STRANDED DNA-BINDING PROTEIN, FROM THE NOVIKOFF HEPATOMA, WHICH STIMULATES DNA POLYMERASE (MEETING ABSTRACT).

Koerner TJ, Meyer RR
University of Cincinnati, Cincinnati, OH, 45221
Fed Proc; 41(3):1196 1982

Single-stranded DNA-binding proteins (SSB) are thought to play important roles in DNA replication and repair. We have isolated and purified to homogeneity, a novel SSB from the rat Novikoff ascites tumor which has properties distinct from other mammalian SSBs. The protein binds cooperatively, but weakly, to single-strand DNA; it is capable of denaturing duplex DNA as determined by nuclease S1 sensitivity and by electron microscopy, and will catalyze helix destabilization of poly(dA-dT) (poly(deoxyadenylate-thymidylate)) at very low temperatures. The protein is a single polypeptide of Mr 48,000 as determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, gel filtration and glycerol gradient sedimentation. The amino acids composition differs from any other eukaryotic SSB so far described, but like these other binding proteins, the Novikoff hepatoma SSB is not high in basic amino acids. This SSB stimulates the activity of DNA polymerase, and this stimulation appears to be enhanced further by the presence of a DNA-dependent ATPase. The Novikoff hepatoma SSB thus plays a role as an accessory protein for DNA synthesis in vitro. (no Refs)

53. DEFECTIVE DNA ENDONUCLEASE ACTIVITY ON ANTHRAMYCIN TREATED DNA IN XERODERMA PIGMENTOSUM AND MOUSE MELANOMA CELLS.

Lee DE, Okorodudu AO, Lambert WC, Lambert MW
Dept. Pathology, New Jersey Medical Sch., Newark, NJ, 07103
Biochem Biophys Res Commun; 107(1):395-402 1982

The endonucleolytic activities of nine nonhistone chromosomal proteins isolated from xeroderma pigmentosum (complementation group A) cells (XPA) and their normal counterparts, and from lymphoblastoid and Cloudman mouse melanoma cells, were assayed using anthramycin (AM)-treated circular duplex PM2 DNA. The binding of AM to DNA was determined spectrophotometrically. A DNA enodnuclease activity which was markedly increased against AM-treated DNA in the nonhistone chromatin protein of normal cells was absent from the nuclei of both XPA lymphoblastoid and Cloudman mouse melanoma cells. These results indicated the presence of an endonuclease with marked specificity for AM-DNA in normal human chromatin that is inactive in these other cell types. Other recent results have indicated that in XPA lymphoblastoid cells and mouse melanoma cells, this same chromatin-associated enzyme fraction has markedly increased activity against untreated, linear, duplex DNA. Thus, there may be more than one abnormality in this enzyme activity. (38 Refs)

EFFECTS OF EXOGENOUS AGENTS ON CHROMOSOMES

54. A SCHEDULE TO DEMONSTRATE RADIATION-INDUCED SISTER CHROMATID EXCHANGES IN HUMAN LYMPHOCYTES.

Chaudhuri JP
Laboratorium fur Experimentelle Radiologie, D-8042 Neuherberg bei Munchen, W. Germany
Radiat Environ Biophys; 20(3):223-229 1982

In view of the known poor response of sister chromatid exchange (SCE) to radiation, a schedule was developed involving the use of caffeine to demonstrate radiation-induced SCE. Other variables included control of the volume of medium, phytohemagglutinin stimulation, and bromodeoxyuridine treatment. With the use of this schedule, a dose-dependent increase in the frequency of radiation-induced SCE was observed. (31 Refs)

55. THE PRODUCTION OF CHROMOSOME ABERRATIONS IN CHINESE HAMSTER FIBROBLASTS BY GAMMA AND NEUTRON RADIATION.

Roberts CJ, Holt PD
Environmental and Medical Sciences Div., Atomic Energy Res. Establishment, Harwell, Didcot, OX11 ORA, England
Int J Radiat Biol; 41(6):645-656 1982

Chromosomal aberrations were scored in V79/4 Chinese hamster fibroblasts exposed to 60Co gamma-rays and to fast neutrons produced from the 9Be(d,n)(10) B reaction. In order to avoid problems with the variation of aberration induction with the phase of the cell cycle, the cells were irradiated in stationary phase, where they are concentrated in the G1 phase of the cycle. The rbe for the production of dicentrics was 2.7 +-0.2 at a neutron dose of 2.0 Gy; the rbe of the 'one-hit' component of response was 6.4 +-1.1. These rbe values are much lower than those reported for primary human lymphocytes. Graphs of the proportion of cells without a dicentric, centric-ring or acentric fragment, as a function of dose, corresponded closely to the survival curves of the cells, which had been obtained previously, for both radiations. (Author abstract) (26 Refs)

56. SENSITIZATION OF MOUSE L CELLS TO ULTRAVIOLET LIGHT BY LOW AMOUNTS OF BROMODEOXYURIDINE.

Thomas GH, Maloney MA, Cleaver JE
Lab. Radiobiology and Environmental Health, Univ. California, San Francisco, San Francisco, CA, 94143
Radiat Res; 91(1):145-154 1982

The effect of substitution of bromodeoxyuridine (BrdUrd) for thymidine in the DNA of mouse L929 cells on their sensitivity to UV light was studied, and the number of cell divisions needed before sensitivity is lost was determined. A similar degree of sensitization was obtained with all proportions from 5-27% BrdUrd; partial sensitization was evident with 2% BrdUrd. The maximum sensitization of 4-5 fold occurred at greater than or = 5% BrdUrd. The presence of bromouracil in DNA produced photochemical reactions in DNA as a result of UV irradiation that were observed as single-strand breaks in alkaline sucrose gradients; the number of breaks was substitution-dependent. Cells left to grow in BrdUrd-less medium lost their sensitivity to UV as number of divisions increased. The cells maintained the same population doubling time during this period, and acquired normal UV sensitivity by 7-10 doublings. Some degree of sensitization by growth in BrdUrd was still observed as long as cells retained at least one chromosome containing BrU; it did not matter which chromosome. The present results suggest why sensitization of tumors by infusion with BrdUrd can be observed in vivo with very small and variable amounts of BrdUrd found in DNA, since the amount of BrdUrd required for sensitization is so small. (29 Refs)

57. EFFECT OF COCULTIVATION ON THE LEVELS OF SPONTANEOUS AND INDUCED SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER CELLS.

Rainaldi G, Luccini F, Mariani T
Istito di Mutagenesi e Differenziamento C.N.R., Via Svezia, 10, 56100-Pisa, Italy
J Cell Physiol; 112(2):281-283 1982

Levels of spontaneous and induced sister chromatid exchanges (SCE) were investigated in Chinese hamster cells (line V79/AP4) cultivated in the presence or absence of human cells (C5R0 normal human fibroblasts or xeroderma pigmentosum cell line XP25R0 fibroblasts). V79/AP4 cells were grown exponentially then exposed to UV light or ethylmethane sulfonate (EMS). SCE were determined in homogeneous cell populations (hamster:hamster) and heterogeneous cell populations (hamster:human). Cocultivation of hamster cells with human cells resulted in a reduction of the spontaneous level of SCE and in the level of SCE induced by UV light and EMS. When XP cells were used as a probe instead of normal human fibroblasts, it was shown that XP cells were equally effective in lowering the SCE of Chinese hamster cells damaged either by UV or EMS. The reduction appeared to depend strongly on cell density: culturing the same total amount of cells on larger dishes resulted in a disappearance of the reduction effect. Replacement of human fibroblasts with hamster cells did not affect the influence of cell density on SCE reduction; however, when damaged hamster cells were used, the level of SCE was not lowered. Use of cocultivation is suggested for investigating SCE formation processes. (19 Refs)

58. RELATIONSHIP BETWEEN SPECIFIC DNA BASE METHYLATION AND INDUCTION OF CYTOTOXICITY, SISTER-CHROMATID EXCHANGES AND CHROMOSOME ABERRATIONS IN CHINESE HAMSTER CELLS (MEETING ABSTRACT).

Medcalf AS, Connell JR
Michigan State University, East Lansing, MI, 48824
Proc Am Assoc Cancer Res; 23:256 1982

An investigation into the relationship between specific DNA purine methylation and induction of cytotoxicity, sister-chromatid exchanges (SCE) and chromosome aberrations in Chinese hamsters cells (V79) was carried out. Density-inhibited cells were treated with either N-[14C] methyl-N-nitrosourea (MNUA) or [14C] dimethyl sulphate (DMS) and then incubated in the density-inhibited state for various times before being assayed for the three biological end-points. At equitoxic doses of MNUA and DMS, we observed similar SCE frequencies and similar chromosome aberration frequencies. However, MNUA reacted to a far greater extent than DMS at the O-6 atom of guanine, while both agents produced similar levels of 3-meA (methyladenine) and similar levels of 7-meG (methylguanine). Colony-forming ability, as a function of incubation time, was inversely correlated with 3-meA levels in DNA, particularly during the initial 4-8 hr of post-methylation incubation. A decrease in SCE frequency was observed during incubation after treatment, but no significant variation in chromosome aberration frequency was discernable with length of incubation. The results suggest that monofunctional methylating-agent induced cytotoxicity, SCEs and chromosome aberrations are not primarily a consequence of O6-meG formation in DNA and that cytotoxicity and SCE induction may be more dependent on methylation of the N-3 atom of adenine. No specific adduct could be correlated with induction of chromosome aberrations. (no Refs)

59. THE ROLE OF ANEUPLOIDY INDUCTION IN DIETHYLSTILBESTROL-INDUCED CELL TRANSFORMATION (MEETING ABSTRACT).

Barrett JC, Tsutsui T, Cummings T, Wong A, McLachlan JA
National Institute of Environmental Health Sciences, Research Triangle Park, NC, 27709
Proc Am Assoc Cancer Res; 23:129 1982

Gene mutations, changes in chromosome structure (aberrations) and chromosome number (aneuploidy) are possible types of genetic changes in neoplastic transformation. We reported that diethylstilbestrol (DES) induces morphological and neoplastic transformation of Syrian hamster embryo (SHE) cells in culture without induction of measurable gene mutations at two loci. We have now examined whether DES induces chromosomal alterations in asynchronous and synchronous cultures of SHE cells at doses which induce cell transformation. DES (0.01-1.0 ug/ml) induced significant levels of aneuploidy but not chromosome aberrations in asynchronous cultures. The majority (90-95%) of metaphases from control cultures had a diploid number of chromosomes, but 4-9% were polyploid and 1-2% were aneuploid around the diploid number. Highly synchronized cultures were treated with 1 ug/ml DES for 3 hr periods during different phases of the cell cycle. Cell transformation occurred in cultures treated in mitosis but not in those treated in early or late S phase. Aneuploidy induction also occurred in cultures treated in mitosis. No increase in chromosome aberrations was observed in any of the treated groups. Malignant cell lines derived from DES treated cultures were aneuploid with near diploid chromosome numbers. These data along with the observations of aneuploid DNA content in dysplastic lesions of offspring of women exposed to DES suggest that induction of aneuploidy may be important in the carcinogenicity of DES. (1 Ref)

60. THE PERSISTENCE OF MICRONUCLEI IN PERIPHERAL BLOOD ERYTHROCYTES: DETECTION OF CHRONIC CHROMOSOME BREAKAGE IN MICE.

Schlegel R, MacGregor JT
United States Dept. Agriculture, Western Regional Res. Center, 800 Buchanan St., Berkeley, CA, 94710
Mutat Res; 104(6):367-369 1982

Following eight ip injections of 0.2 mg/kg triethylene-melamine (TEM), bone marrow RBC of male Swiss-Webster mice exhibited a steady increase in the incidence of micronuclei. This elevated level did not return to normal values until approx 30 days after TEM was discontinued. It was concluded that micronucleated RBC induced by a bone-marrow clastogen accumulate in the peripheral blood of mice and there is very little or no selective removal of these aberrant cells from circulation. Application of this method for assessment of in vivo chromosome breakage in chronic or subchronic toxicity studies is suggested. (7 Refs)

61. EFFECTS OF POLYCYCLIC HYDROCARBONS ON THE INDUCTION OF CHROMOSOMAL ABERRATIONS IN ABSENCE OF AN EXOGENOUS METABOLIC ACTIVATION SYSTEM IN CULTURED HAMSTER CELLS.

Kochhar TS
Dept. Biology, Kentucky State Univ., Frankfort, KY, 40601
Experientia; 38(7):845-846 1982

The effect of carcinogenic polycyclic hydrocarbons on the chromosomes of cultured Chinese hamster cells was investigated. Contrary to earlier reports it was observed that benz(a)anthracene, benzo(a)pyrene, 7,12-dimethylbenz(a)anthracene and 3-methylcholanthrene were effective in causing chromosomal aberrations without any exogenous metabolic activation. Duration of incubation with these agents may be the cause of difference in results. Importance of prolonged treatment period is discussed. (Author abstract) (9 Refs)

62. CYTOGENETIC STUDIES ON RAT TUMOR DEVELOPMENT: AN IN VIVO - IN VITRO APPROACH TO CHARACTERIZE CHROMOSOME INVOLVEMENT IN RAT NEOPLASIA AND CELL LINES.

Haag MM
University of Cincinnati, Cincinnati, OH
Diss Abstr Int [B]; 42(10):3917-B 1982

A single transplacental dose of the carcinogen, ethyl-nitrosourea (ENU), administered to pregnant rats late in gestation results in a high incidence of neurogenic tumors in the adult offspring. Cytogenetic studies of cell lines from neurogenic tumors induced by ENU show that chromosome number 4 is consistently involved. Using this animal model, the role of chromosome abnormalities in neoplasia was studied by monitoring the specificity and development of chromosome number 4 abnormalities. Analysis of 10 neurogenic lines from virally induced tumors showed abnormalities of chromosomes number 1, number 2 and number 3. Chromosome number 4 was not involved in abnormalities in these lines suggesting that there is a specificity of etiologic agent and number 4 alterations. Six out of nine cell lines from ENU-induced tumors of non-neurogenic origin had numerical and/or structural abnormalities of number 4 indicating the lack of tissue specificity for number 4 abnormalities in ENU oncogenesis. Preneoplastic cultured trigeminal nerve tissue from ENU-exposed animals of various ages was sequentially monitored for chromosome abnormalities as the cultures developed neoplastic potential in vitro. Analysis of 16 cell lines initiated from the preneoplastic ENU-induced trigeminal nerve tissue showed that the lines could acquire tumorigenic potential in vitro regardless of chromosome abnormalities observed. Cell lines with normal chromosomes as well as lines having abnormalities other than number 4 developed tumorigenic potential in vitro. The results of these studies indicate that chromosome number 4 abnormalities appear later in the development of tumors, are not tissue specific and are associated only with ENU oncogenesis; however, the abnormalities are secondary to the tumorigenic potential of the cell lines. (no Refs)

63. CYTOGENETIC ANALYSIS OF BONE MARROW OF RATS TREATED WITH MITOXANTRONE HYDROCHLORIDE, AN ANTINEOPLASTIC AGENT (MEETING ABSTRACT).

Dulak L, Manandhar M, Iatropoulos MJ, Noble JF
Medical Research Division, American Cyanamid Co, Pearl River, NY, 10965
Proc Am Assoc Cancer Res; 23:134 1982

Mitoxantrone hydrochloride, an anthraquinone type antineoplastic agent was tested in in vivo cytogenetic tests. In the first test, male rats were given mitoxantrone intraperitoneally at doses of 2.0, 1.0 or 5.0 mg/kg/day for five consecutive days. Bone marrow was examined on the sixth day. An increased percentage of cells with chromosomal aberrations was noted at all dose levels. Aberrations were induced at all doses and significantly more at the two higher doses and included chromatid and chromosome - breaks as well as multiple and complex aberrations. These aberrations were similar to those produced by other antineoplastic agents. A second cytogenetic study was conducted under conditions approximating the clinical usage. Male rats were given 0.3 mg/kg mitoxantrone intravenously once and bone marrow examined 1 and 21 days following treatment. A second group of rats was given 0.3 mg/kg mitoxantrone twice, 21 days apart and bone marrow was examined 21 days after the second dose. An increased percentage of cells with chromosome aberrations was noted one day following treatment. The aberrations found were similar to those noted in the first study. However, by 21 days after treatment (either after one or two doses) the percentage of cells with aberrations had fallen to control level, indicating that the clastogenic effects observed immediately following dosing were not cumulative or persistent. (no Refs)

64. SEQUENTIAL CHANGES IN DIPLOID RAT LIVER EPITHELIAL CELLS TREATED WITH AFLATOXIN B1 IN CULTURE (MEETING ABSTRACT).

Iype PT, Currens MJ, Herring A, Kelley SP, McMahon JB, Ray-Chaudhuri R, Malan-Shibley L
National Cancer Institute-Frederick Cancer Research Facility, Frederick, MD, 21701
Proc Am Assoc Cancer Res; 23:290 1982

Experiments were performed to analyze the chronology of the onset of transformation markers induced in rat liver cells by the hepatocarcinogen, aflatoxin B1 (AFL). A well-characterized, diploid liver epithelial cell line which exhibited no transformation markers was used at the tenth subculture. Three groups were studied. Group 1 consisted of untreated cells, Group 2, cells receiving a single treatment, and Group 3 cells given multiple exposures to the compound. The markers followed included altered karyology, loss of response to an hepatic proliferation-regulating protein (HPI), induced multinucleation by cytochalasin B, the presence of gamma-glutamyl transpeptidase (gamma-GT) and alpha-fetoprotein, the ability to bind concanavalin A coupled with agarose beads, the formation of colonies in soft agarose, and the growth of tumors in rats. Group 1 exhibited none of these characteristics for the 34 week duration of the study, except that aneuploid cells were seen in the population at 23 weeks. The earliest change seen in Groups 2 and 3 was a shift to a hyperdiploid karyology and the occurrence of marker chromosomes, which was followed by a loss of response to HPI, expression of gamma-GT, induction of multinucleation, growth in soft agar and tumorigenicity. Markers were observed at an earlier time in Group 3 compared with Group 2. The sequential appearance of these different markers might be indicative of progressive changes leading to malignancy. (no Refs)

65. MUTAGENICITY TESTS WITH DOMPERIDONE IN VITRO AND IN VIVO.

Vanparys P, Fabry L, Leonard A, Marsboom R
Lab. Toxicology, Veterinary Dept., Janssen Pharmaceutica, Turnhoutseweg 30, B-2340 Beerse, Belgium
Toxicol Lett; 12(2/3):215-222 1982

Induction of chromosome damage by domperidone was investigated in vivo by a micronucleus test on Albino Swiss mice and in a dominant lethal test on both male and female mice. In vitro chromosome damage was assessed in short-term cultures of human lymphocytes. No chromosome aberrations were observed in mammalian cells in vivo and in vitro, even in the presence of microsome enzymes. (13 Refs)

66. SISTER CHROMATID EXCHANGES IN HUMAN LYMPHOCYTES TREATED WITH COMBINATIONS OF CYTOTOXIC DRUGS.

Clare MG, Blain E, Taylor JH
Univ. Dept. Radiotherapy, Regional Radiotherapy Centre, Cookridge Hosp., Leeds LS16 6QB, England
Eur J Cancer Clin Oncol; 18(6):533-544 1982

Lymphocytes from peripheral blood of either 'normal' donors or patients with cancer stimulated to divide in culture medium containing 5-bromo-2'-deoxyuridine. During 74 hr of incubation, the cells were exposed to single agents or to permutations of two combinations of chemotherapeutic drugs, namely nitrogen mustard, vincristine, procarbazine and prednisolone or cyclophosphamide and methotrexate. Only mustine and cyclophosphamide (activated and not activated) increased the frequency of sister chromatid exchanges (SCE). Neither vincristine, procarbazine or prednisolone with mustine, nor methotrexate with cyclophosphamide altered the number of SCEs expected from the use of mustine or cyclophosphamide alone. There was no difference in the response of cells from cancer patients and 'normal' subjects to the drugs. If the drugs of these two regimens do interact with one another to enhance the amount of subcellular damage, this is not manifested by changes in the number of SCEs in human lymphocytes in vitro. (Author abstract) (39 Refs)

67. VARIATION IN THE SENSITIVITY OF HUMAN LYMPHOCYTES TO DNA-DAMAGING AGENTS MEASURED BY SISTER CHROMATID EXCHANGE FREQUENCY.

Crossen PE
Cancer Society of New Zealand, Cytogenetics Unit, Christchurch Hosp., Christchurch, New Zealand
Hum Genet; 60(1):19-23 1982

The bromodeoxyuridine (BrdU) Giemsa technique was used to determine incidence of sister chromatic exchanges (SCEs) and changes in cellular proliferation in peripheral blood lymphocytes from normal donors.Blood cells were exposed to mitomycin C (0.01 ug/ml), proflavine (0.4 ug/ml), and 3H-uridine (3.7 kilobecquerels/ml). All lymphocytes treated with mitomycin C showed an increase in SCEs over the baseline level, with 75% of the donors showing a doubling of SCE rate. No chromosomal or chromatid aberrations were observed. Mitomycin C treatment resulted in an increase of first division cells, and a decrease in third division cells, while the number of second division cells was unchanged. Proflavine was less efficient than mitomycin C in inducing exchanges; no samples showed doubling of SCE rate. No chromosomal or chromatid aberrations were evident, but numbers of third division metaphases were decreased and the number of first division metaphases were correspondingly increased. 3H-Uridine was least efficient in inducing SCEs, but all cultures treated with 3H-uridine exhibited numerous chromosome and chromatid aberrations, and showed a dramatic reduction in third division metaphases and a corresponding increase in first and second division metaphases. There was considerable variation among individuals in response to all three treatments, with some individuals' lymphocytes not responding at all. Thus, the BrdU Giemsa technique may be useful in determining effective treatment schedules for cytostatic agents and for determining individual susceptibility to mutagens and carcinogens. (16 Refs)

68. SISTER CHROMATID EXCHANGES IN LYMPHOCYTES OF A PATIENT TREATED WITH CYCLOPHOSPHAMIDE AND VINCRISTINE FOR NON-HODGKIN'S LYMPHOMA.

Ohtsuru M, Ishii Y, Takai SI, Kosaki G
Second Dept. Surgery, Osaka Univ. Medical Sch., 1-1-50 Fukushima, Fukushima-ku, Osaka 553, Japan
Gan; 73(3):433-438 1982

Sister chromatid exchanges (SCEs) were investigated in lymphocytes from an adult patient treated with cyclophosphamide (CTX) and vincristine (VCR) for non-Hodgkin's lymphoma. The treatment consisted of iv injection of CTX (1 g) followed immediately by injection of VCR (2 mg). The patient was treated 6x at weekly intervals, except for two irregular intervals of 35 and 48 days, respectively, as the second and the fourth intervals. Before the initiation of the therapy, the SCE frequency in the patient was 9.9 +-3.5 per cell, which is not significantly different from those of healthy controls and other cancer patients not given chemotherapy. After the first injection, the SCE frequency increased rapidly with time, reaching a peak of 33.4 +-4.6 per cell in 24 hr, and then gradually decreased, returning to a nearly normal level of 12.5 +-4.2 per cell on the 7th day. Similar cycles of rapid increase and slow decrease in the SCE frequency were observed after each of the subsequent five injections, resulting in a gradual rise in the basal and the maximal levels of the SCE values. Oral administration of CTX (150 mg/day) for about a mo during the second interval slightly increased the SCE value from 16.1 +-3.1 to 22.4 +-6.2 but injections of vincristine alone at a dose of 2 mg twice during the fourth 45-day interval did not affect the gradually decreasing trend in the SCE frequency. In the 5th mo after the termination of the therapy, the SCE value returned to the untreated level. (Author abstract) (12 Refs)

69. INDUCTION OF SISTER-CHROMATID EXCHANGES IN HUMAN LYMPHOCYTES BY EXTRACTS OF PARTICULATE EMISSIONS FROM A DIESEL ENGINE.

Lockard JM, Kaur P, Lee-Stephens C, Sabharwal PS, Pereira MA, McMillan L, Mattox J
(c/o Pereira) Health Effects Res. Lab., United States Environmental Protection Agency, Cincinnati, OH, 45268
Mutat Res; 104(6):355-359 1982

The sister-chromatid exchange (SCE) assay was used to determine the ability of an extract of the organic components of the particulate matter of diesel exhaust to damage human chromosomes. The results were compared to those obtained with benzo(a)pyrene (BaP). The potency of the diesel extract was approx one-fifth that of BaP with a 54-hr exposure time and no exogenous activation. Extract of organic constituents of particles from diesel exhaust is potentially genotoxic to humans. (15 Refs)

70. THE EFFECT OF CIGARETTE SMOKE CONDENSATES ON THE FREQUENCY OF SISTER CHROMATID EXCHANGE (SCE) IN HUMAN LYMPHOCYTES IN VITRO.

Lin Z, Lu D, Zhang B, Zhao H, Deng C
Dept. Pediatrics, Affiliated Hosp., Guangzhou Medical Coll., Guangzhou, People's Republic of China
Zhonghua Yufangyixue Zazhi; 15(5):284-286 1981

The effects of smoke condensates from three brands of Chinese cigarettes on SCE were studied in human lymphocytes in vitro. Results showed that at 0.25 mg smoke condensate per 5 ml culture medium the frequency of SCE was increased. The increase was more marked at higher concentrations. The significance of increased SCE frequency in relation to DNA damage and carcinogenesis is discussed. (9 Refs) (In CHI)

GENERAL REVIEWS

71. DNA REPAIR: A LABORATORY MANUAL OF RESEARCH PROCEDURES. VOLUME 1-PART B.

Friedberg EC, Hanawalt PC
Dept. Pathology, Stanford Univ., Stanford, CA
DNA Repair: A Laboratory Manual of Research Procedures. Volume 1 - Part B. New York, Marcel Dekker Inc., 360 pp., 1981.

DNA repair technology is reviewed with emphasis on application for research and development purposes. Measurement of DNA repair synthesis by autoradiography, equilibrium sedimentation, photolysis of bromouracil, benzoylated naphthoylated diethylaminoethyl cellulose, and metabolic inhibitors is described. DNA strand breaks can be measured by sedimentation in alkaline sucrose gradients, alkaline elution, alkaline denaturation and hydroxyapatite chromatography, electron microscopy, gel electrophoresis, end labeling, and nitrocellulose membrane filtration. DNA daughter strand repair can be measured by postreplication repair in prokaryotes and mammalian cells, alkaline elution, and bromouracil photolysis. Biological parameters of DNA repair are discussed with respect to measurement of colony-forming ability and mutagenesis in diploid human cells and Chinese hamster cells; genetic markers for mutagenesis studies in mammalian cells; screening of mutagens by inhibition of DNA synthesis; measurement of sister chromatid exchange in mammalian cells; and purification, plaque assay, and inactivation of human adenoviruses 2 and 5. (491 Refs)

72. REPAIR RESPONSES TO DNA DAMAGE: ENZYMATIC PATHWAYS IN E COLI AND HUMAN CELLS.

Hanawalt PC, Cooper PK, Ganesan AK, Lloyd RS, Smith CA, Zolan ME
Dept. Biological Sciences, Stanford Univ., Stanford, CA, 94305
J Cell Biochem; 18(3):271-283 1982

Known responses to damaged DNA in bacteria and mammalian systems are reviewed and recent approaches to the study of DNA repair is described. Topics discussed include constitutive and inducible repair of DNA, the role of chromatin structure in DNA repair, and activities of endonuclease V of bacteriophage T4 and properties of the cloned denV gene. (66 Refs)

73. PRECLINICAL TOXICOLOGY PROFILE OF ACYCLOVIR: AN OVERVIEW.

Tucker WE
Dept. Toxicology and Experimental Pathology, Wellcome Res. Lab., Research Triangle Park, NC, 27709
Am J Med; 73(1A):27-30 1982

Numerous and extensive toxicologic studies of acyclovir using animal and in vitro assays indicated a low order to toxicity for this antiviral nucleoside analog. Primary cytotoxic effects occurred only at extremely high drug concentrations in plasma or tissue cultures. This correlates well with the high selectivity of the drug for herpes viruses and its low toxicity for uninfected cells in tissue culture. Secondary toxicity in the form of precipitation of acyclovir crystals in the lower nephron of the kidney occurred after rapid intravenous bolus injection causing transient impairment of renal function in the dog and obstructive nephropathy in the rat. These secondary effects were related to the relatively low solubility of acyclovir in the urine. Dermal and ophthalmic formulations were well-tolerated. No significant primary irritation nor systemic toxic manifestations were associated with the application of these materials. A test in guinea pigs gave no indication that acyclovir has sensitization potential. Acyclovir had no effect on reproductive processes or prenatal, perinatal, or postnatal development of offspring in studies with rats, rabbits, and mice. Positive results occurred in 2 of 11 in vitro mutagenicity assays. These involved chromosomal damage at extremely high drug concentrations. In contrast, no evidence of chromosomal damage occurred in three in vivo assays at nontoxic dosage levels and under conditions more relevant to clinical use of the drug. While one of two cell transformation assays gave positive results, no oncogenic potential for acyclovir was indicated by lifetime carcinogenicity bioassays in rats and mice. Numerous in vitro and in vivo assays gave no indication that acyclovir might significantly alter immunologic responses at clinically relevant doses. (Author abstract) (7 Refs)

74. AVIAN LEUKEMIA VIRUSES ONCOGENES AND GENOME STRUCTURE.

Graf T, Stehelin D
Inst. Virology, German Cancer Res. Center, In Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
Biochim Biophys Acta; 651(4):245-271 1982

Avian leukemia viruses, with emphasis mainly on defective leukemia viruses (DLVs), are reviewed. Oncogenic spectra of chicken-derived DLVs and the turkey-derived reticuloendotheliosis virus (REVT) are presented. Transformation specificity of DLVs in vitro, genetic content and genome structure of avian erythroblastosis virus (AEV), avian myeloblastosis virus (AMV)-type, myelocytomatosis virus strain 29 (MC29)-type, REVT, expression of RNA and proteins in cells infected with AEV, AMV, MC29, and OK10, genetics of DLVs including mutants in transforming functions and recovered viruses, conservation of cellular oncogene (c-onc) genes through evolution, chromosomal localization and structure of c-onc genes, and expression of c-onc genes in normal cells, mechanisms of transformation by avian leukosis viruses (ALV) and DLVs, the promoter insertion hypothesis of ALV-leukemogenesis, hematopoietic target cell specificity and possible role of c-onc genes in the DLV-leukemogenesis, and transformation of nonhematopoietic cells by DLVs are discussed. Origin of DLVs is reviewed, including reverse transcription of encapsidated viral and cellular RNAs, viral promoter insertion, recombination of integrated provirus with a c-onc gene, and integration of proviruses around a c-onc gene. (167 Refs)

OTHER RELATED STUDIES

75. DIFFERENCES IN PATTERNS OF COMPLEMENTATION OF THE MORE COMMON GROUPS OF XERODERMA PIGMENTOSUM: POSSIBLE IMPLICATIONS.

Giannelli F, Pawsey SA, Avery JA
Paediatric Res. Unit, Guy's Hops., London SE1 9RT, England
Cell; 29(2):451-458 1982

Xeroderma pigmentosum of Groups A, C and D shows complementation differing in kinetics, dependence on the dose of wild-type alleles and dependence on protein synthesis. Such differences suggest that XP-A, -C and -D carry mutations at different loci. The product of the first of these loci (factor A) is present in significant excess in normal fibroblasts, seems to turn over rapidly and may be a dimer or higher polymer. The products of the other two loci (factors C and D) do not seem to be present in significant excess in the cytoplasm of normal fibroblasts, but factor C may accumulate abnormally in XP-D. Factors C and D turn over slowly (D more than C) and they do not move freely from the cell nucleus. Factors A and C, at least, seem to act directly and not via gene regulation. (Author abstract) (17 Refs)

76. SEPARATION AND CHARACTERIZATION OF HUMAN TUMOR CELLS ON A DISCONTINUOUS PERCOLL GRADIENT (MEETING ABSTRACT).

Kopper L, Casillo S, Rustum Y, Slocum H, Frankfurt O, Takita H
Roswell Park Memorial Institute, Buffalo, NY, 14263
Proc Am Assoc Cancer Res; 23:114 1982

Since the therapeutic response of solid tumors is influenced by the interaction of different subpopulations, studies have been conducted to separate and characterize subsets of cells from human specimens. Suspensions released sequentially by mechanical (M) and enzymatic (E) methods were centrifuged at 1000xg for 30 min at 4 degrees through a Percoll gradient. Fractions were characterized as to their viability (trypan blue exclusion) and cellular composition. Separations of 9 solid tumors (3 lungs, 2 sarcoma, 1 each of colon, melanoma, ovarian and kidney) indicated that viability increased with increasing density, although the overall viability resembled that of the unseparated population. Median cell recovery was 50% for M and E released cells. In both E and M suspension the fractions with 1.02-1.06 density were enriched in tumor cells; 1.08 density contained most leukocytes (lymphocytes, plasma cells, polymorphonuclear cells), and red blood cells were at greater than 1.1 density. In two cases where the unseparated suspension possessed a diploid and aneuploid population determined by flow cytometry it was possible to separate fractions enriched with aneuploid cells. Preliminary results indicate that different cloning efficiency can be obtained in different fractions. Thus, Percoll separation of tumor cells can lead to a better understanding of tumor cell heterogeneity. (no Refs)

77. A PROGNOSTIC FACTOR ANALYSIS FOR USE IN DEVELOPMENT OF PREDICTIVE MODELS FOR RESPONSE IN ADULT ACUTE LEUKEMIA.

Keating MJ, Smith TL, Gehan EA, McCredie KB, Bodey GP, Freireich EJ
Dept. Developmental Therapeutics, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner, Houston, TX, 77030
Cancer; 50(3):457-465 1982

The pretreatment characteristics of 325 adults with acute leukemia who were treated at the M D Anderson Hospital between 1973 and 1977 have been evaluated to assess their value as prognostic indicators. The patient population includes all patients treated with an anthracycline (Adriamycin or rubidazone), cytosine arabinoside, vincristine, and prednisone during the time period. Most patients had one of the variants of acute myelogenous leukemia (75%), and the remaining patients had acute lymphoblastic leukemia (16%) or undifferentiated leukemia (8%). Twenty-one factors were found to be significantly associated with probability of obtaining a complete response. In addition to characteristics previously known to provide prognostic information such as age, temperature status at the start of treatment, morphology, the presence of Auer rods, sex, and hemoglobin level, we identified the presence of a documented antecedent hematologic disorder and the finding of insufficient metaphases on cytogenetic analysis using the squash technique as being major prognostic variables. In addition, the pretreatment biochemical characteristics of hypoalbuminemia and elevated blood urea nitrogen and creatinine were found to adversely influence prognosis. The prognostic significance of factors such as the leukocyte count and platelet count, identified in earlier studies, was not confirmed in this group of patients. From this natural-history analysis predictive models for response have been developed using multivariate logistic regression techniques. One of these models has been used to evaluate the effect of morphology, treatment, and cytogenetic pattern on response to the combination of drugs used. (Author abstract) (24 Refs)

78. STANDARDIZATION OF THE SISTER CHROMATID EXCHANGE TECHNIQUE IN HUMAN LYMPHOCYTES FOR MUTAGEN AND CARCINOGEN TESTING.

Kamlesh S
Western Michigan University, Kalamazoo, MI
Diss Abstr Int [B]; 42(10):3948-B 1982

The differential staining of chromosomes with the use of 5-bromo-2'-deoxyuridine (BUdr) is used extensively to study sister chromatid exchange (SCE). The frequency of SCEs increases significantly in the presence of mutagenic and carcinogenic agents. Hence, the BUdR technique (commonly referred to as the SCE technique) has been useful as a diagnostic tool to test for mutagenic and carcinogenic agents. Investigators have used differential staining to obtain a baseline incidence of SCEs in human lymphocytes; but their results show a wide variation. This makes the testing of mutagenic and carcinogenic agents problematic. A more basic problem encountered in using the SCE technique is that the yield of differentially stained chromosomes is too low for analytical purposes. The present study is designed to standardize the differential staining technique so that the problem of low yield can be overcome. The three specific objectives of this research, are to: (a) establish culture conditions that yield a high frequency of metaphase spreads; (b) determine the time of initiation of DNA synthesis; and (c) establish staining conditions that yield an adequate number of differentially stained chromatids for SCE analysis. (no Refs)

79. PSORALENS ARE NOT MUTAGENIC IN THE SALMONELLA ASSAY (MEETING ABSTRACT).

Rao TK, Allen BE, Cox JT
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Med Pediatr Oncol; 10(1):100 1982

Psoralens are the most notable photosensitizing agents with clinical use for the treatment of skin diseases. Photochemical interaction with the pyrimidine bases of DNA is the basis for their biological activity, which raises the possibility of adverse effects such as toxicity, mutagenicity, carcinogenicity and chromosomal aberrations. Sufficient evidence exists to show that 8-methoxypsoralen (8-MOP), followed by exposure to near UV light (NUV) causes tumors in albino mice, sister chromatid exchange in lymphocytes, and mutations in microbial assays. Psoralens are not adequately studied in the Salmonella assay. Our studies indicated a lack of mutagenic activity for 8-MOP and trioxsalen even when metabolically activated, which is contrary to the report of Bridges and Mottershead that 8-MOP caused frameshift mutations in the dark. Exposure to NUV following treatment with 8-MOP or trioxsalen of stationary or log phase cells did not show mutagenic activity. However, a dose-dependent (7.5-25 x 10(3) J/m2 from a Westinghouse F40BLB lamp) cytotoxicity was noted with strains deficient (TA98 and TA100) for UV-excision repair. Strains capable of UV-excision repair (TA1978 and TA1975) were less sensitive in the cytotoxicity assay. This suggests a genetic nature of the damage. These studies indicate the inability of the Ames Salmonella assay to detect 8-MOP (a possible carcinogen) as a mutagen. (1 Ref)

80. GENOTOXIC EFFECTS OF SUNLIGHT-ACTIVATED WASTE WATER IN CULTURED MAMMALIAN CELLS.

Strniste GF, Chen DJ, Okinaka RT
Genetics Group, Life Sciences Div., Los Alamos Natl. Lab., Los Alamos, NM, 87545
JNCI; 69(1):199-203 1982

Cultured Chinese hamster ovary cells were incubated with dilutions of an oil shale retort process water and exposed to natural sunlight. An enhancement of sevenfold to ninefold was seen in photoinduced cytotoxicity (by a colony-forming assay) and mutagenicity [at the hypoxanthine phosphoribosyltransferase (HPRT) locus] for cells pretreated with the process water compared to effects seen in cells exposed to sunlight only. Significant photoinduced cytotoxicity was also observed in cultured human skin fibroblasts when exposed to the process water before being exposed to near UV (NUV) radiation. The mutation frequencies (determined for the HPRT locus) induced by the process water and NUV radiation were as great as those frequencies seen for far UV light alone. Increases in genotoxicity were observed in excision repair-deficient xeroderma pigmentosum skin fibroblasts when compared to the responses seen in normal cells. Risks to health resulting from the phototransformation of these oil shale retort process waste waters are unassessed at this time. (Author abstract) (19 Refs)

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